HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE

Digitized by the Internet Archive
in 2016 with funding from
The National Endowment for the Humanities and the Arcadia Fund

https://archive.org/details/westernjournalof1231cali

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE

SHELVE UNDER

JUL 16 '75
REC'D

JUL 31 '75
STACKS
CIRCULATES

THE WESTERN Journal of Medicine

VOLUME 123 • NUMBER 1 **JULY 1975**

1 *Pediatric Renal Transplantation*
YESHAWANT B. TALWALKAR, MD, MARVIN H. HARNER, MD, JAMES E. MUSGRAVE, MD, RUSSELL K. LAWSON, MD, and ROBERT A. CAMPBELL, MD

7 *Sleep Apnea Syndrome—Can It Induce Hemodynamic Changes?*
CHRISTIAN GUILLEMINAULT, MD, FREDERIC L. ELDRIDGE, MD, F. BLAIR SIMMON, MD, and WILLIAM C. DEMENT, MD

17 *Antenatal Diagnosis of an XXX Female—A Dilemma for Genetic Counseling*
LAWRENCE R. KRONE, BS, LORRAINE L. PRICHARD, PHN, CHRISTY L. BRADSHAW, BS, OLIVER W. JONES, MD, RAYMOND M. PETERSON, MD, and BARBARA K. DIXSON, RN, MN

MEDICAL PROGRESS
22 *Advice to Travelers* ELIZABETH BARRETT-CONNOR, MD

MEDICAL STAFF CONFERENCE
31 *Pulmonary Vascular Disease* Chief Discussant: HOMER BOUSHEY, MD

41 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Chest Diseases*

47 EDITORIALS • *Malpractice and Social Change* • *Medical Information for Travelers* • *The Motivation and Conscience of the Physician* • *Pulmonary Vascular Disease*

CASE REPORTS
51 *Runaway Pacemaker—A Serious and Unresolved Problem*
FREDERICK W. KUNKEL, MD, KURT NEUMANN, MD, and MELVIN M. SCHEINMAN, MD

53 *Transmural Myocardial Infarction in a Young Man with Normal Coronary Arteriograms*
W. V. R. VIEWEG, CDR, MC, USN, and D. G. TRETHEWAY, LCDR, MC, USN

56 *Mondor's Disease* EUGENE C. WEINSTEIN, MD

58 *A Splash in the Joint* BRUCE C. GILLILAND, MD, and JAMES H. CALDWELL, MD

60 LETTERS TO THE EDITOR

TRAUMA ROUNDS
64 *Transfusion Practices in Trauma Patients* Chief Discussant: GEORGE F. SHELDON, MD

FROM A MEDICAL STUDENT
69 *Medicine, Critical Science and the Real World* TEE L. GUIDOTTI, MD

PROFESSIONAL LIABILITY
71 *Res Ipsa Loquitur* L. WARD WISEMAN, MD

INFORMED CONSENT
76 *Are Research Subjects Really Informed?*
AMELIA L. SCHULTZ, PhD, GERALDINE P. PARDEE, MN, and JOHN W. ENSINCK, MD

SPECIAL ARTICLE
81 *A Survey of Newborn Intensive Care Centers in California* WARREN E. HAWES, MD, MPH

85 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, ALASKA, AND IDAHO**
(See Advertising Page 37)

01%-OUT 062675 SU8050060 66
UNIV OF MARYLAND
HEALTH SCIENCES LIB SERIAL
111 SOUTH GREEN ST
BALTIMORE MD 21201

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND

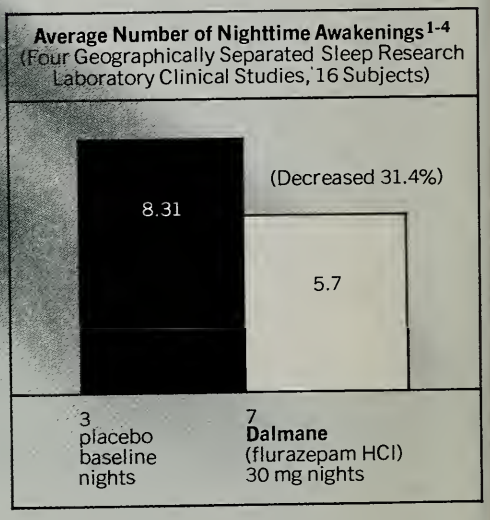
JUL 16 '75 REC'D

JUL 31 '75 CIRCULATES

Would sleep with fewer nighttime awakenings benefit your patients with insomnia?

Highly predictable results for your patients with trouble staying asleep...

...can be obtained with Dalmane (flurazepam HCl). As shown below, Dalmane significantly reduces nighttime awakenings:[1-4]



X77-361

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

August 21-22—**Multidisciplinary Approach to Cancer Treatment.** UCSF at Children's Hospital, San Francisco. Thursday-Friday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** See Radiology and Pathology, September 27-28.

MEDICINE

July 21-24—**Primary Care Dermatology.** STAN. Monday-Thursday.

August 2—**Hypoglycemia: What It Is and Isn't.** UCLA. Saturday.

August 13-17—**Advanced Seminar in Dermatology.** UCI at Newporter Inn, Newport Beach. Wednesday-Sunday.

September 5-6—**San Diego County Heart Association—25th Annual Symposium.** Friday-Saturday. 13 hrs. $20, members; $25, non-members. Contact: Cathy Ware, Prog. Dir., SDCHA, 3640 5th Ave., San Diego 92103. (714) 291-7454.

September 12-14—**Practical Approaches to Arthritis.** UCI at Marriott Hotel, Newport Beach. Friday-Sunday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18-June.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 18 hrs. $25.

September 26-27—**Infectious Disease—8th Annual Fall Meeting.** Children's Hospital of Oakland at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Calori, Medical Staff Office, Children's Hospital Medical Center, Oakland 94609. (415) 654-5600.

September 27-28—**Workshop in Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 1-3—**San Francisco Heart Association—45th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. 18 hrs. $50. Contact: Evelyn Berggren, San Francisco Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 1-4—**Laboratory Advance in Internal Medicine.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

October 3—**Kidney Foundation of Northern California—Symposium.** Hyatt Union Square, San Francisco. Friday. Contact: Michael H. Humphreys, MD, Prog. Chr., Kidney Foundation of No. Calif., UC Renal Center, S. F. General Hospital, Bldg. 100, Rm., 350, San Francisco 94110.

October 3-4—**Cardiology Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley C. Gach, Coord., So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

October 9-12—**California Society of Internal Medicine.** Vacation Village, San Diego. Thursday-Sunday. Contact: Carol H. Handley, Exec. Dir., SCIM, 1412 Central Towers, 703 Market Street., San Francisco 94103. (415) 362-1548.

October 10—**Current Trends in Dermatologic Therapy.** PMC. Friday.

October 15-17—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

October 15-19—**American Association for Clinical Immunology and Allergy.** Riviera Hotel, Palm Springs. Wednesday-Sunday. Contact: Howard Silber, AACIA, P.O. Box 912, DTS, Omaha, Neb. 68101. (402) 558-5345.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 24-25—**Symposium on Respiratory Care.** Fresno Community Hospital. Friday-Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

October 26-30—**American College of Chest Physicians—41st Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Thursday, Contact: Alfred Soffer, MD, Exec. Dir., ACCP, 911 Busse Highway, Park Ridge, Ill. 60068. (312) 698-2200.

OBSTETRICS AND GYNECOLOGY

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 25-27—**Fall Symposium in Obstetrics and Gynecology—Oncology, Endocrinology and Infertility.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

September 27-October 4—**Workshops in Gynecologic Oncology, High Risk Pregnancy and Endocrinology-Infertility.** UCSF at Maui, Hawaii. One week.

October 5-10—**Pacific Coast Obstetrical and Gynecological Society.** Pebble Beach. Sunday-Friday. Contact: Melvin W. Breese, MD, 1133 SW Market St., Portland, Ore. 97201.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

October 15-19—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 31 hrs. $15 for members; $25, non-members. Contact: Ms. Dee Davis, Exec. Sec., PCFS, 5410 Wilshire Blvd., Suite 600, Los Angeles 90036. (213) 937-5514.

October 24-25—**Perinatal Neurology.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday.

October 31—**Advances in Gynecology.** Northern California Ob-Gyn Society at Sacramento. Friday. Contact: Solon Barbis, MD, 1816 Professional Dr., Sacramento 95825.

PEDIATRICS

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 24-25—**Brennemann Memorial Lectures—32nd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

PSYCHIATRY

July 26-27—**A Biofeedback Workshop.** UC, Santa Cruz. Saturday-Sunday. 15 hrs. $75. Contact: Darla Chadima, Cont. Ed. Specialist, Applied Sciences Bldg., UC Extension, Santa Cruz 95064. (408) 429-2971.

September 20—**Psychotherapy.** UCD, Central California Psychiatric Society and Fresno County Dept. of Mental Health at Rodeway Inn, Fresno. Saturday. Contact: Central Calif. Psych. Society, 451 Parkfair Dr., Suite 4, Sacramento 95825. (916) 488-4320.

October 7-28—**Introduction to Behavioral Medicine.** UCLA. Tuesday evenings.

RADIOLOGY AND PATHOLOGY

August 10-15—**The Pathology and Radiology of Bone and Joint Diseases.** UCLA at UC Residential Conference Center, Lake Arrowhead. Sunday-Friday.

September 27—**Current Topics in Diagnostic Radiology.** Southern California Permanente Medical Group at Marriott Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 27-28—**Nuclear Medicine.** UCLA. Saturday-Sunday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** UCLA. Saturday-Sunday.

October 8-12—**American Society of Therapeutic Radiologists.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Sheila McGing, Exec. Sec., ASTR, 20 N. Wacker Dr., Room 2920, Chicago, Ill. 60606.

SURGERY AND ANESTHESIOLOGY

July 17-18—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

July 19—**Phacoemulsification with Insertion of an Intraocular Lens.** St. Mary's Hospital and Medical Center, San Francisco. Saturday. $200. Contact: St. Mary's Hospital and Medical Center, 2200 Hayes St., San Francisco 94117.

August 6-10—**Urology—Annual Advanced Seminar.** UCLA at UC Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 7-8—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 17-29—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 3-November 19—**Acupuncture for Control and Management of Musculo-Skeletal Pain.** UCLA. Wednesday evenings.

September 6-13—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 7-19—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Thursday evenings. Contact: Linda Alperstein, Coordinator, Cont. Med. Ed., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

September 27-28—**American Society of Anesthesiologists—Regional Refresher Course.** Disneyland Hotel, Anaheim. Saturday-Sunday. 8 hrs. $50. Contact: John S. Hattox, Jr., MD, ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

September 27-28—**Workshop in Dermatologic Surgery.** See Medicine, September 27-28.

September 28-October 1—**Western Neurosurgical Society.** Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Wednesday. Contact: John S. Tytus, MD, 1118 9th Ave., Seattle 98101. (206) 223-6641.

October 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 13-17—**American College of Surgeons—Clinical Congress.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: C. Rollins Hanlon, MD, 55 E. Erie St., Chicago, Ill. 60611.

October 24-25—**Retinal Symposium.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

October 26-30—**Western Orthopedic Association.** Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. Contact: H. Jacqueline Martin, Exec. Sec., WOA, 1970 Broadway, Suite 1235, Oakland 94612. (415) 893-1257.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

July 11-20—**Associated Alumni-California College of Medicine—Annual Convention.** Hawaii. 10 days. Contact: Kay Stewart, Exec. Dir., Associated Alumni, CCM, 710 N. Euclid, Suite 210, Anaheim 92801. (714) 776-8820.

July 14-18—**Postgraduate Institute for Emergency Physicians—Symposium I.** UCSD. Monday-Friday.

August 2—**Hypoglycemia: What It Is and Isn't.** See Medicine, August 2.

August 11-15—**Postgraduate Refresher Course—18th Annual.** USC at Sheraton-Waikiki Hotel, Honolulu. Monday-Friday.

August 11-15—**Postgraduate Institute for Emergency Physicians—Symposium II.** UCSD. Monday-Friday.

August 14-17—**Association of Philippine Practicing Physicians In America—4th Annual Convention.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: Lucito G. Gamboa, 35 Bradford Lane, Oak Brook, Ill. 60521. (312) 654-1126.

August 17-21—**American Society for Pharmacology and Experimental Therapeutics.** UCD. Sunday-Thursday. Contact: Dr. Keith F. Killam, Jr., Chr., Dept. of Pharmacology, UCD. (916) 752-3421.

August 20-24—**Family Practice Refresher Course—2nd Annual.** UCLA and Santa Mónica Medical Center. Wednesday-Sunday.

August 24-29—**Family Practice Refresher Course—3rd Annual.** UCD. Sunday-Friday.

September 2-7—**Family Practice Review Course—6th Annual.** UCI at Newporter Inn, Newport Beach. Tuesday-Sunday.

September 3-November 19—**Acupuncture for Control and Management of Musculo-Skeletal Pain.** See Surgery, September 3-November 19.

September 9-October 28—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland Hospital. Tuesday evenings.

September 14-19—**Emergency Medical Care Review.** UCD at Pajaro Dunes. Sunday-Friday.

September 15-19—**New Ways to Foster Health and Human Well-Being.** Health Training Resources Center, California Dept. of Health, at 1625 Shattuck Ave., Berkeley. Monday-Friday. Contact: Health Training Resources Ctr., Calif. Dept. of Health, 2151 Berkeley Way, Berkeley 94704.

September 18-19—**Experimental Approaches to the Study on Manipulation Therapy.** UCI at Center for Health Education, Long Beach. Thursday-Friday.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** See Medicine, September 19-20.

September 22-26—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

September 23-November 25—**Yoga: Clinical Applications and Techniques.** UCLA at 1620 Preuss Rd., W. Los Angeles. Tuesday, 7:30-10:00 p.m. 25 hrs. $85.

October 2-4—**Western Occupational Medical Association.** Sheraton Harbor Isle, San Diego. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 6-10—**Primary Care.** STAN. Monday-Friday.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** San Francisco General Hospital (7th) and UCSF (8th). Tuesday-Wednesday. Visiting professor will be D. J. Weatherall, MD, Radcliffe Infirmary, Oxford, England. October 7—**Molecular Pathology of the Thalassaemia Disorders.** October 8—**Clinical and Genetic Aspects of the Control of Foetal Haemoglobin Production.** Contact: Susan Nutter, S.F. General Hospital, 1001 Potrero Ave., San Francisco 94110. (415) 648-8200, ext. 404.

October 8-11—**Medical Society of the United States and Mexico—23rd Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: Virginia E. Bryant, Exec. Sec., 333 W. Thomas Rd., Suite 207, Phoenix, Ariz. 85013.

October 9-11—**Wound Healing—Theory and Practice.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

October 9-30—**Introduction to Humanistic Medicine.** UCLA. Thursdays.

October 11—**American Geriatrics Society, Inc., Western Division—4th Annual Meeting.** Newporter Inn, Newport Beach. Saturday. $35. Contact: Irving Hirshleifer, MD, 1080 N. Indian Ave., Palm Springs 92262. (714) 325-5044.

October 16-17—**Immunology for the Practicing Physician.** UCSF. Thursday-Friday.

October 17—**Antiplatelet Drugs and Thrombosis.** PMC at Miyako Hotel, San Francisco. Friday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

(Continued on Page 41)

"Antiacid" action for ulcer patients...

one of the many things you need in an anticholinergic.

Pro-Banthīne is considered adjunctive in total peptic ulcer therapy that may include diet, conventional antacids, bed rest, and other supportive measure

Pro-Banthīne is provided in several different dosage forms which will meet virtually any clinical need. It is just as versatile in filling patient needs, among which are:

"Antiacid" action—Pro-Banthīne® (propantheline bromide) reduces gastri secretory volume and resting total and free acid.

"Analgesic" action—Pro-Banthīne helps to control the acid-spasm-pain complex.

Vigorous anticholinergic action—Pro-Banthīne® Vials, 30 mg., are for intramuscular or intravenous use when prompt and vigorous anticholinergic action is required.

Mild anticholinergic action—Pro-Banthīne® Half Strength, 7.5 mg. tablets, for more exact adjustment of maintenance dosage in mild to moderate gastrointestinal disorders.

Pro-Banthīne
(propantheline bromide)

a good option in peptic ulcer

Pro-Banthīne®
brand of
propantheline bromide

Indications: Pro-Banthīne is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution. Fever and possibly heat stroke may occur due to anhidrosis.

Overdosage may cause a curare-like action, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted. Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthīne.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may occur as well as mydriasis and blurred vision. In addition the following adverse reactions have been reported: nervousness, drowsiness, dizziness, insomnia, headache, loss of the sense of taste, nausea, vomiting, constipation, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult oral therapy is one 15-mg. tablet with meals and two at bedtime. Subsequent adjustment to the patient's requirements and tolerance must be made.

How Supplied: Pro-Banthīne is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680 481

(Continued from Page 39)

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

NEUROLOGY

June 7-8—**Oregon Neurosurgical Society Annual Meeting.** Jantzen Beach Thunderbird, Portland. Contact: Michael Mason, MD, 2525 N.W. Lovejoy, Portland 97210.

OF INTEREST TO ALL PHYSICIANS

August 15-16—**John Tomlin Memorial Cancer Lectures.** Medford. Contact: American Cancer Society, Oregon Division, Inc., Jackson County Unit, P.O. Box 698, Medford 97501, phone 779-6091.

Sept. 10-14—**Oregon Medical Association Scientific Session and House of Delegates.** Portland, Hilton Hotel. Contact: James A. Kronenberg, Oregon Medical Association, 2164 S. W. Park Place, Portland 97205, phone 226-1555.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

July 30-August 1—**Idaho Medical Association Annual Meeting.** Wednesday-Friday. The Lodge, Sun Valley, Idaho. Contact: Armand L. Bird, Exec. Director, 407 W. Bannock St., Boise, Idaho 83702.

August 11-12—**Sports Medicine Workshop.** Monday-Tuesday. Graves Building, University of Washington. 13¼ hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 3-5—**Western Conference of the American Lung Associations.** Wednesday-Friday. Olympic Hotel, Seattle. Contact: Janet Chalupnik, Washington Lung Association, 216 Broadway E., Seattle 98102. (206) 329-4411.

September 8-10—**Topics in Clinical Microbiology.** Monday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. 9 hrs., $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 10-12—**Recent Advances in Infectious Diseases—American College of Physicians.** Wednesday-Friday. Olympic Hotel, Seattle. 16 hrs. Members, FACP $100; non-members, $150; ACP Associates, $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 12-13—**American College of Physicians Regional Meeting with Washington State Society of Internal Medicine.** Friday-Saturday. Olympic Hotel, Seattle. 5½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 14-17—**North Pacific Pediatric Society Annual Meeting.** Sunday-Wednesday. Rosario, Orcas Island, Washington. Contact: Bernard P. DeJong, MD, Secretary, 3195 Granville St., Vancouver 9, B.C., Canada. (604) 738-2102.

September 15-16—**Liver and Cancer.** Monday-Tuesday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 17-19—**Physical Therapy Training Institute.** Wednesday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 19-22—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan Knudson, Exec. Director, 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110.

September 26-27—**Arthritis Days '75.** Friday-Saturday. Olympic Hotel and Univ. of Wash. Health Sciences Center, Seattle. 9 hrs. Fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 26-27—**Review of Basic OB-GYN.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Div. of CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 1-June 9, 1975—**Internal Medicine Review.** Wednesday evenings, 6 p.m.-8 p.m., 35 weeks. Univ. of Wash. Health Sciences Center, Seattle. 70 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 2-4—**Montana State Medical Association Annual Meeting.** Thursday-Saturday. Fairmont Hot Springs Resort, Gregson, Montana. Contact: G. Brian Zins, Exec. Director, 2021 11th Ave., Suite 12, Helena, MT 59601.

October 4-5—**Skin Surgical Techniques.** Saturday-Sunday. Univ. of Wash. Health Sciences Center, Seattle. Limited to 50. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (296) 543-1050.

October 13-17—**Treating the Untreatable—Univ. of Washington School of Medicine's Eastern Washington Circuit Course.** Pullman, 13; Walla Walla, 14; Tri-Cities, 15; Yakima, 16; Wenatchee, 17. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 14-19—**American Society of Clinical Hypnosis Annual Meeting.** Tuesday-Sunday. Washington Plaza Hotel, Seattle. Contact: Ernest T. Guy, Exec. Director, East Devon Ave., Suite 218, Des Plaines, IL 60018. (312) 297-3317.

October 16-17—**Team Effort in the Management of Cancer.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 17-18—**Washington State Heart Association Symposium.** Friday-Saturday. Olympic Hotel, Seattle. Fee to be determined. Contact: De Loris Savage, R.N., Wash. State Heart Assoc., 333 1st Ave. W., Seattle 98119. (206) 285-2415.

October 30-31—**Office Management of Chronic Pain.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Sattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Ames Company
Diastix 10
Armour Pharmaceuticals Co.
Letter 17
Ayerst Laboratories
Premarin 6, 7
Boehringer Ingelheim Ltd.
Combipres 11, 12, 13, 14, 15, 16
Books Received 17
Burroughs Wellcome Co.
Neosporin Ointment 27
Classified 31, 36
Compton Foundation 36
Eli Lilly & Company, Inc.
Manufacturer of Darvocet-N 100 and Darvon Compound-65 26
Mead Johnson Laboratories
Vasodilan 4
Merck Sharp & Dohme
Triavil 18, 19, 20
Pharmaceutical Manufacturers Association
Drug Bioequivalence 34, 35
Roche Laboratories
Dalmane ..... 2nd Cover and page 1
Gantanol 8, 9
William H. Rorer, Inc.
Camalox 22, 23
Maalox ..... 4th Cover
G. D. Searle & Co.
Pro-Banthine 40, 41
Security Pacific Bank 5
Smith Kline & French Co.
Dyazide 3
Union Bank 21
The Upjohn Company
Medrol 32, 33
Warren-Teed Pharmaceuticals Incorporated
Modane ..... 3rd Cover
Wyeth Laboratories
Bicillin/Wycillin 24, 25
Ovral 28, 29, 30

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANTIMICROBIAL THERAPY—Second Edition—Benjamin M. Kagan, MD, Director, Department of Pediatrics, Consultant in Infectious Disease, Department of Medicine, Cedars-Sinai Medical Center; Professor of Pediatrics, University of California, Los Angeles, School of Medicine; With Contributions by 73 Authorities. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 482 pages, $22.00.

CLINICAL PERINATOLOGY—Edited by Silvio Aladjem, MD, Associate Professor, Department of Obstetrics and Gynecology, University of Illinois at the Medical Center, Chicago; and Audrey K. Brown, MD, Professor of Pediatrics, Director, Division of Pediatric-Hematology-Oncology, Medical College of Georgia, Augusta. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, MO (63103), 1974. 492 pages, $39.50.

CURRENT MEDICAL DIAGNOSIS AND TREATMENT—1975—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, Research Associate, Palo Alto Medical Research Foundation; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1975. 1044 pages, $13.50.

DIAGNOSTIC AND THERAPEUTIC AIDS IN UROLOGY—Henry Bodner, MD, Associate Clinical Professor, Department of Surgery (Urology), Loma Linda University School of Medicine, White Memorial Hospital Division, Los Angeles; In Collaboration with John S. Arconti, Jr., MD, Formerly Clinical Instructor, Department of Surgery (Urology), UCLA Center for the Health Sciences; Allan H. Howard, MD, Associate Clinical Professor, Department of Surgery (Urology), University of California Medical Center, Irvine; and Robert O. Pearman, MD, Associate Professor, Department of Surgery (Urology), UCLA Center for the Health Sciences, Los Angeles. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62703), 1974. 332 pages, $24.75.

THE GODS OF LIFE—Neil Elliott, Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1974. 180 pages, $7.95.

HOW MUCH FOR HEALTH?—Senator Warren G. Magnuson and Elliot A. Segal, MD, Assistant Dean, Yale Medical School. David McKay Company, Inc., 750 Third Avenue, New York City (10017), 1974. 210 pages, $7.95.

HOW TO TEACH YOUR CHILDREN ABOUT SEX—Harry Preston; With introduction by Gordon Anderson, MD. Books for Better Living, 21322 Lassen Street, Chatsworth, CA (91311), 1974. 176 pages, $1.25 (Paperback).

IN DEFENSE OF THE BODY—An Introduction to the New Immunology—Roger Lewin, PhD, Science Editor, **New Scientist.** Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 146 pages, $2.50 (Paperback).

INTRODUCTION TO CLINICAL EXAMINATION—Edited by John Macleod, Head of University Department of Medicine, Western General Hospital, Edinburgh; E. B. French, Reader, University Department of Medicine, Western General Hospital, Edinburgh; and J. F. Munro, Member Clinical Teaching Staff and University Department of Medicine, Western General Hospital, Edinburgh. Longman Inc., 72 Fifth Avenue, New York City (10011), 1974. 99 pages, $5.00 (Paperback).

LIFESAVING, RESCUE AND WATER SAFETY—Prepared by The American National Red Cross. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 240 pages, $2.25.

THE MALNOURISHED MIND—Elie A. Shneour, MD. Anchor Books, Anchor Press/Doubleday, Garden City, NY (11530), 1975. 209 pages, $2.95 (Paperback).

MONOGRAPH ON PROFESSIONAL STANDARDS REVIEW ORGANIZATIONS—Proceedings from PSRO—An Educational Forum, September 21, 1974, Department of Continuing Education in Health Sciences, University Extension; the School of Medicine; and the School of Public Health, University of California, Los Angeles—Raymond D. Goodman, MD, MPH, Editor. UCLA Extension, Room 540R, PO Box 24902, Los Angeles, CA (90024), 1975. 94 pages, $5.00. (Make checks payable to The Regents of the University of California, and mail order to PO Box 24901, Dept. K, UCLA Extension, Los Angeles, CA 90024.)

PUBLIC EDUCATION ABOUT CANCER—Recent Research and Current Programmes—International Union Against Cancer (UICC), 1974. 73 pages: Individual copies available free-of-charge; bulk orders of 5 or more copies: 3 Swiss francs per copy. Orders should be addressed to: The Managing Editor, International Union Against Cancer, 3, rue du Conseil Général, 1205 Geneva, Switzerland.

REFERRING THE PSYCHIATRIC PATIENT—A Guide for the Physician—Larry R. Kimsey, MD, Clinical Assistant Professor of Psychiatry; and Jean L. Roberts, MD, Clinical Instructor of Psychiatry, The University of Texas Southwestern Medical School at Dallas. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62703), 1973. 80 pages, $6.95.

The 2 most widely prescribed sodium levothyroxine (T_4) products are:

LETTER®
(Sodium levothyroxine, Armour) Tablets

SYNTHROID®
(Sodium levothyroxine) Flint Tablets

LETTER® IS 10% LOWER IN PRICE THAN SYNTHROID®*

Armour Pharmaceutical Company
Phoenix, Arizona 85077

*Armour's published list price to pharmacies for LETTER is 10% less than the Flint published price for Synthroid in bottles of 100 of the same strength. Pharmacy charges to the patient will vary from pharmacy to pharmacy, depending on individual locations, policies and services offered.

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping...."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to start! Did you find anything wrong with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP & DOHME For a brief summary of prescribing information, please turn to the following page.

Refer to: Talwalkar YB, Harner MH, Musgrave JE, et al: Pediatric renal transplantation. West J Med 123:1-6, Jul 1975

THE WESTERN
Journal of Medicine

Pediatric Renal Transplantation

YESHAWANT B. TALWALKAR, MD, MARVIN H. HARNER, MD, JAMES E. MUSGRAVE, MD, RUSSELL K. LAWSON, MD, *and* ROBERT A. CAMPBELL, MD, *Portland*

Thirty-one children received 38 kidney transplants from 22 live and 16 cadaver donors. Among the 31 patients, 25 received one transplant each, 5 received two transplants each and 1 received three transplants. Peritoneal or hemodialysis (or both) was carried out in 22 patients, with an average dialytic maintenance of 12 weeks before transplantation. Posttransplant immunosuppressive therapy included prednisone and azathioprine. Antilymphocyte globulin was administered to 33 recipients as adjunctive immunosuppressive therapy.

At present, 23 patients have functioning allografts, 3 are on hemodialysis and 5 are dead. Of 22 live kidney transplants, 18 are presently functioning two months to 14 years after transplantation with an average of 36 months. Of 16 cadaver kidney transplants, 5 are presently functioning 9 to 57 months after transplantation with an average of 32 months. Actuarial live donor allograft survival for one year was 76 percent, for two years was 66 percent and for three years was 64 percent. Cadaver allograft survival was 50 percent, 40 percent and 40 percent, respectively.

Complications were urologic and infection related. Of nine recipients with sustained hypertension, in six the condition was due to chronic rejection, while in one it was due to recurrence of the original disease in the allograft. Linear growth was measured in 15 children who were less than 14 years of age at the time of transplantation and in whom allografts survived more than one year. Maximum average linear growth velocity occurred during the first year after transplantation. Our experience indicates pediatric renal transplantation can be successfully used in the treatment of terminal renal failure.

PEDIATRIC RENAL TRANSPLANTS constitute 20 percent of the transplants done at the University of Oregon Medical School. This report details our experience in 31 children who received 38 kidney transplants. All but two transplants were done between 1968 and 1973, with an average of six transplants per year. It is of special interest that in three patients with cystinosis, noted on functional and morphological studies, recurrence of cystinosis in the transplanted kidney has not been seen. Measurement of linear growth in 15 children has shown that the maximum average linear growth velocity occurred during the first year after transplantation. Ultimate height achieved after transplant remains a concern.

From the Departments of Pediatrics and Urology, University of Oregon Health Sciences Center, Portland.

Submitted, revised, January 23, 1975.

Reprint requests to: Y. B. Talwalkar, MD, Renal-Metabolic Unit, Department of Pediatrics, University of Oregon Health Sciences Center, Portland, OR 97201.

Material and Management

Table 1 categorizes the causes of renal failure in our patients. At the time of transplantation the ages of recipients ranged from one week to 18

years. In the 38 transplants done, 22 kidneys were from living related donors and 16 from cadaver donors.

Dialysis was carried out in 22 patients before initial transplant. Peritoneal dialysis was done alone in 3 patients and begun before hemodialysis in 5 patients. Hemodialysis alone was done in 14 patients. Dialytic maintenance before transplant ranged from two weeks to six months with an average of 12 weeks.

Histocompatibility antigen (HL-A) tissue typing was carried out in all donors and recipients except for the two cases in which transplants were done before 1968. One recipient and her identical twin donor in 1969 had negative cross autogenous skin grafts.

Azathioprine and corticosteroids were given for immunosuppression. Azathioprine was given in an initial dose of 5 mg per kg of body weight per day and then tapered to 1 to 2 mg per kg of body weight per day within two weeks after transplant for maintenance. Dosage was adjusted to maintain the leukocyte count above 4,000 per cu mm. Methylprednisolone, 500 mg, was given intravenously at operation and on the first postoperative day. Oral administration of prednisone, 30 mg per sq meter of surface area per day, was then started and tapered over 12 months to 8 to 10 mg per sq meter of surface area per day for maintenance.

Antilymphocyte globulin (ALG) was administered as adjunctive immunosuppressive therapy to 21 of 22 recipients of kidneys from living related donors and to 12 of 16 recipients of kidneys from cadavers. The ALG was prepared in horses, goats or turkeys and was given intramuscularly at a dose of 8 mg of protein per kg of body weight.

TABLE 1.—*Causes of Renal Failure Leading to Transplantation*

Chronic glomerulonephritis	5
Focal sclerosing glomerulonephritis	3
Membranoproliferative glomerulonephritis	2
Intersitial nephritis	1
Rapidly progressive glomerulonephritis	1
Obstructive uropathy/pyelonephritis	5
Renal dysplasia	3
Cystinosis	3
Alport's syndrome	2
Familial juvenile nephronophthisis	2
Hemolytic uremic syndrome	2
Polycystic kidneys	1
Medullary cystic disease	1
TOTAL	31

The schedule of administration was daily for four weeks, then three times weekly for four weeks, twice weekly for four weeks and finally once weekly for four weeks.

Acute rejection was treated with intravenous methylprednisolone, 20 mg per kg of body weight, and either Actionomycin D, 15 micrograms (μg) per kg of body weight, or in our later experience, local allograft irradiation in doses of 150 roentgens (R) every other day. In most instances, the patient received from 450 to 600 R in the initial series of treatments. Additional treatments were given in some cases to a total dose of no more than 1,000 R to the kidney. Mild episodes of acute rejection were treated with intravenous administration of methylprednisolone alone.

Results

Allograft Function

Table 2 gives information about 31 patients who received a total of 38 kidneys. Of these, 25 patients had one transplant, 5 patients had two transplants and 1 patient had three transplants. Table 3 tabulates initial allograft function in the living related donor and cadaver kidney recipients.

In the 22 recipients who received a living related donor kidney, 18 of the kidneys are functioning two months to 14 years after transplant, with an average of 36 months. Creatinine clearances range from 36 to 113 ml per min corrected to a surface area of 1.73 sq meters with an average of 72. Of the 4 patients in whom kidneys failed to function, 1 is dead, 1 has had a cadaver kidney transplant and 2 are on hemodialysis awaiting cadaver donors.

Of the 16 recipients who received a cadaver kidney, the kidneys in 5 are presently functioning nine to 57 months after transplant, with an average of 32 months. Creatinine clearances range from 47 to 106 ml per min corrected to a surface area of 1.73 sq meters, with an average of 65. Six cadaver kidneys failed to function after transplant (Table 3). Of the remaining 10 cadaver kidneys that functioned after transplant, 5 eventually failed (1 due to acute rejection, 3 due to chronic rejection and 1 due to recurrence of the original disease in the transplanted kidney). Among the 11 patients who received a total of 16 cadaver kidneys, 7 patients are alive and 4 are dead. In the 7 surviving patients, 5 have a functioning cadaver kidney, one has a living related donor kidney and 1 is on hemodialysis.

TABLE 2.—*Summary of Patients*

No.	*Diagnosis*	*Age at Transplant*	*Donor*	*Months Function*	*Present Ccr/1.73 m²*	*Comment*
1	CGN	12 years	twin	196	79	Doing well, married
2	CGN	18 years	father	68	47	Ureteral necrosis-reimplant; doing well
3	HUS	9 months	mother	..	..	Dead
4	Ob. U.	12 years	father	53	36	Vesicocutaneous fistula closed; chronic rejection and hypertension
5	Cystinosis	6 years	father	50	66	Ureteral necrosis-reimplant; doing well
6	Cystinosis	8 years	mother	46	80	Hypertension
7	Dysplasia	9 years	mother	43	39	Doing well
8	CGN	11 years	mother	40	113	Doing well
9	CGN	14 years	mother	26		Doing well; followed in Montana; serum creatinine 1.3 mg%
10	Cystinosis	9 years	mother	23	46	Doing well
11	CGN	10 years	mother	21	130	Hydonephrosis 12 months posttransplant-repaired; doing well
12	Medullary cystic	17 years	father	18	49	Hypertension
13	FJN	14 years	mother	16	69	Doing well
14	FJN	11 years	father	12	89	Urine leak-reimplant; hypertension
15	FSGN	12 years	mother	11	87	Doing well
16	MPGN	10 years	mother	10	57	Doing well
17	Ob. U. Chr. pyelo.	15 years	father	..	..	Acute rejection; graft removed; on hemodialysis
18	Chr. pyelo.	13 years	brother	5	101	Doing well; obese
19	FSGN	13 years	mother	2	40	Acute tubular necrosis; hypertension
20	MPGN	12 years	mother	..	..	Acute rejection; graft removed; on hemodialysis
21	HUS	12 months	cadaver	..	..	Dead
22	Dysplasia	17 years	cadaver	12	..	Peri-renal hematoma; chronic rejection; graft removed
		18 years	cadaver	46	65	Doing well
23	Alport's	16 years	cadaver	..	..	Hyperacute rejection
		16 years	cadaver	57	46	Doing well
24	FSGN	4 years	cadaver	57	..	Allograft recurrence; graft removed
		8 years	cadaver	..	..	Acute rejection; on hemodialysis
25	Ob. U.	13 years	cadaver	45	47	Chronic rejection; hypertension
26	Polycystic kidneys	1 week	cadaver	..	..	Hyperacute rejection; dead
27	Dysplasia	9 years	cadaver	13	..	Chronic rejection; graft removed
		10 years	cadaver	9	106	Doing well
28	RPGN	13 years	cadaver	3	..	Acute rejection; dead
29	Alport's	14 years	cadaver	10	61	Doing well
30	Interstitial nephritis	3 years	cadaver	..	..	Acute rejection; graft removed
		3 years	cadaver	10	..	Urine leak; reimplant; chronic rejection; graft removed
		4 years	mother	41	97	Doing well
31	Ob. U.	14 years	father	..	..	Acute rejection; graft removed; gas gangrene abdominal wall; recovered
		14 years	cadaver	..	..	Acute rejection; graft removed; dead; unrelated causes

Ccr/1.73 m² = creatinine clearance corrected to a surface area of 1.73 sq meters
CGN = chronic glomerulonephritis
HUS = hemolytic uremic syndrome
Ob.U = obstructive uropathy
Chr. pyelo. = chronic pyelonephritis
FJN = familial juvenile nephronophthisis
FSGN = focal sclerosing glomerulonephritis
MPGN = membranoproliferative glomerulonephritis
RPGN = rapidly progressive glomerulonephritis

Actuarial survival rates for kidneys from living related donors and from cadavers are given in Chart 1. For kidneys from living related donor, one-year survival was 76 percent, two-year survival was 66 percent and three-year survival was 64 percent. Cadaver kidney survival was 50 percent for one year, 40 percent for two years and 40 percent for three years.

Patient Survival

At present, 23 patients have functioning allografts, three are on hemodialysis and five patients are dead. The patient who has survived for the longest time, the recipient of an allograft from an identical twin, has given birth to a normal infant. Of the five deaths that occurred, one was unrelated to transplantation. All four transplant-related deaths occurred within three months of transplant. Table 4 summarizes the causes of death in our patients.

TABLE 3.—*Initial Allograft Function*

	Living Related		*Cadaver*	
Immediate		9		6
Delayed:				
Acute tubular necrosis	3		..	
Acute rejection	4		2	
Urologic complication	2	9	2	4
No function:				
Hyperacute rejection	..		2	
Acute rejection	3		3	
Urologic complication	1		..	
Technical failure	..	4	1	6
TOTAL		22		16

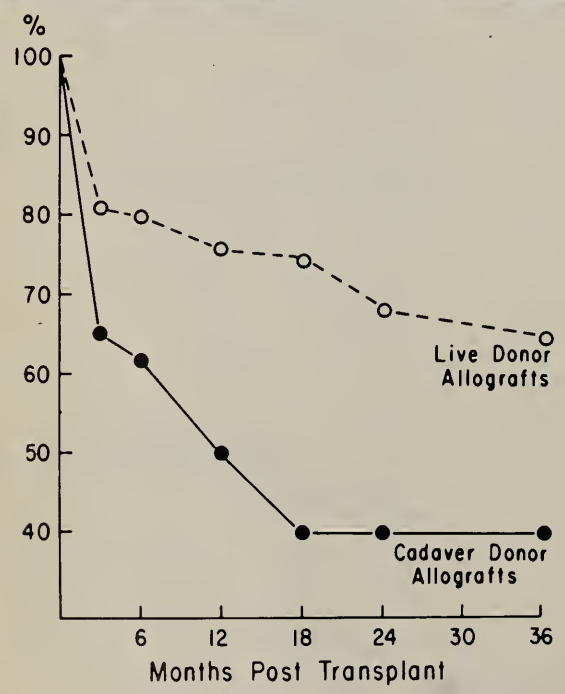


Chart 1.—Allograft survival for living and cadaver donor allografts.

Complications

Urologic complications occurred in seven of the 28 recipients whose kidneys functioned after transplant. These complications were caused by ureteral obstruction in four recipients, perirenal hematoma in one, vesicocutaneous fistula in one and obstructive hydroureteronephrosis at the anastomotic site in one. Details of their management are discussed elsewhere.[1]

Table 5 summarizes the significant infections in our patients. In addition, bacterial urinary tract infection occurred in 16 of the 28 kidneys that functioned after transplant. In five recipients more than one episode of infection occurred. All episodes were controlled with antibiotic or urinary suppressive therapy. Fungal infection of the urinary tract occurred in three recipients, in one of whom it was successfully treated with 5-fluorocytosine for Candida albicans.

Moderate hypertension after the third post-transplant month was recorded in nine recipients when compared with normal percentiles for age.[2] Blood pressure was readily controlled in five recipients, of whom three have chronic rejection. In the other four recipients, blood pressure was poorly controlled and the allografts were removed. In three of these, stenosis of the renal arterial anastomosis or branches of the renal artery was noted, secondary to chronic rejection. In the remaining recipient whose allograft was removed, there was recurrence of the original disease in the transplanted kidney.

Growth

Fifteen children, seven boys and eight girls, below the age of 14 years at the time of transplantation and whose allografts survived more than one year, were studied for linear growth velocity. Increase in linear growth velocity over a six month interval was compared with linear growth at the 50th percentile of a normal child of the same age and sex.[3] Observed linear growth velocity was expressed as percent of the expected linear growth velocity and averaged for both boys and girls at each six month interval (Chart 2). Maximum average linear growth velocity occurred within the first year after transplantation. Thereafter, the growth velocity progressively decreased. Both boys and girls had approximately the same aver-

TABLE 4.—*Cause of Death in Allograft Recipients*

Patient No.	*Age Years*	*Kidney Donor*	*Time After Transplant*	*Cause*
3	9/12	Live	17 days	Pseudomonas and Enterobacter sepsis; bronchopneumonia; purpura; cerebral infarction
21	1	Cadaver	3 days	Candida albicans sepsis; central nervous system hemorrhage; purpura
26	1 wk.	Cadaver	11 days	Hyperacute rejection; renal failure
28	12	Cadaver	90 days	Acute rejection; dysequilibrium syndrome during dialysis
31	14	Cadaver	30 days	Allograft removed; subdural hematoma from fall

TABLE 5.—*Infections*

Patient No.	*Type*	*Organism*	*Outcome*
3	Septicemia	Pseudomonas *plus* Enterobacter	Dead
5	Septicemia *plus* RML pneumonia and UTI	Enterobacter *plus* Candida albicans	Cured
21	Septicemia	Candida albicans	Dead
31	Intrarenal	Aspergillus	Allograft nephrectomy
31	Abdominal wall	Claustridium perfringes	Cured

RML = right middle lobar (pneumonia)
UTI = urinary tract infection

age linear growth velocity. No apparent difference between donor source and linear growth velocity was noted.

Cystinosis Patients

Three patients with cystinosis received transplants from living related donor at 6½, 8 and 10 years of age, respectively. On follow-up renal tubular function studies were done, including 12 hour fluid restriction for urinary concentrating ability and 36 hour ammonium chloride loading for urinary acidification. Results are summarized in Table 6. No pronounced abnormalities of renal tubular dysfunction consistent with recurrence of cystinosis in the allograft were present. In one patient, number 6, in whom impairment of maximum urinary concentrating ability and urinary acidification was present, no other abnormalities suggestive of proximal tubular dysfunction were observed. Both abnormalities could be explained on the basis of distal renal tubular acidosis seen following transplantation.[4]

In two patients, numbers 6 and 10, allograft biopsies were done 31 and 14 months after transplantation, respectively. On routine light microscopy, both biopsy specimens showed normal glomeruli while polarized light microscopy showed no cystine crystals within tubular epithelial cells. Electron microscopy did not show granular material within the glomerular visceral epithelial cells and no hexagonal crystalline inclusions were seen in renal tubular cells. Microdissection of 42 proximal tubules from both biopsies showed no swan-neck deformity.

Discussion

Previous reports have established pediatric renal transplantation as a successful method of therapy for end-stage renal disease.[5-13] In our series, the overall patient survival rate was 84 percent, while 72 percent of patients have functioning allografts. Survival rates for allographs in children with kidneys from living related donors and from cadavers are given in Chart 1 and compare favorably with results in adults for living related and cadaver

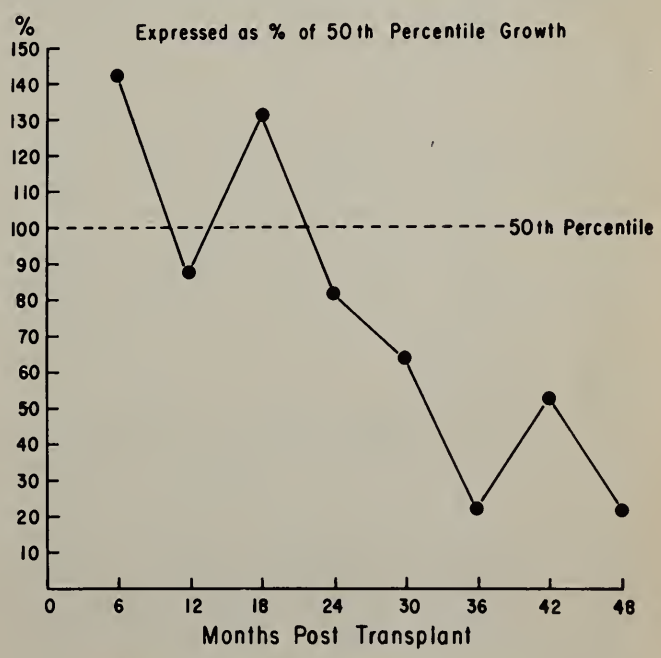


Chart 2.—Average linear growth velocity.

TABLE 6.—*Study of Tubular Function in Cystinosis Patients After Renal Transplantations*

	Normal	Patient Numbers 5	6	10
Months posttransplant		49	44	21
Creatinine clearances-mls/min/1.73 m^2	100-120	62	58	72
Phosphate clearance-mls/min/1.73 m^2	12-18	15.8	16	7.4
Percent tubular reabsorption of phosphate	80-92	76	73	90
24-hour urinary glucose	negative	negative	negative	negative
24-hour urinary protein excretion, in mg. up to	200	270	negative	negative
12-hour fluid restriction test-max. osmolarity, mOsm/L	1,400	1,358	614	1,494
Ammonium chloride loading test:				
Total Dose-250 mEq/sq meter/36 hours				
Control serum bicarbonate, mEq/L		25	21	25
Control urine pH		5.70	6.45	7.11
Lowest serum bicarbonate, mEq/L		10	10	16
Corresponding urine pH		4.64	5.60	5.02
Urinary amino acid screening		normal	very slight-generalized	normal

mls/min/1.73 m^2 = ml per min corrected to a surface area of 1.73 sq meters

donors.[14,15] However, both allograft and patient survival rates are reduced below five years of age.[16] In our series, three of the five patients less than five years of age at the time of transplant were one year old or less and died.

Of the ten chief causes of renal failure leading to renal transplantation reported by the Renal Transplant Registry, glomerulonephritis and pyelonephritis represent 71.3 percent of the total, with glomerulonephritis the leading cause in 57 percent.[14] Various glomerulonephritides and pyelonephritis/obstructive uropathy similarly are the two leading causes in our patients representing 54 percent of the group. However, other causes assume greater prominence in childhood because of their congenital or heritable nature such as renal dysplasia, Alport's syndrome, familial juvenile nephronophthisis (juvenile medullary cystic disease) and cystinosis. Of special interest is cystinosis, an invariably fatal disease when it occurs within the first decade of life. In our series, three patients with cystinosis continue to do well 33 to 60 months after transplant. In these patients, results of renal tubular function studies and of allograft biopsy studies have not suggested recurrence of cystine deposition in the transplanted kidneys.

Normal linear height is often not achieved following transplantation.[17] Corticosteroid therapy has been suggested as a contributing factor in limiting posttransplant growth.[6,18] However, maximum average linear growth velocity occurred within one year following transplant in our patients during the period of highest corticosteroid dosage. Although growth hormone levels are normal,[19] some factor necessary for action of growth hormone may be decreased after the first posttransplant year. All 15 children have remained below the third percentile for height before and after transplantation.

REFERENCES

1. Lawson RK, Talwalkar YB, Musgrave JE, et al: Renal transplantation in children. Read at Western Section of American Urological Association meeting, San Francisco, Apr 1974
2. Moss AJ, Adams FH: Problems of Blood Pressure in Childhood. Springfield, Ill., Charles C Thomas, 1962
3. Meredith HV: Tables 2-5 and 2-6. Percentiles for weight and height—Birth to 18 years, *In* Nelson WE, Vaughan VC III, McKay RJ (Eds): Textbook of Pediatrics, 9th Ed. Philadelphia, W. B. Saunders Company, 1969, pp 42-47
4. Wilson DR, Siddiqut AA: Renal tubular acidosis after kidney transplantation. Ann Intern Med 79:352-361, Sep 1973
5. Williams GM, Lee HM, Hume DM: Renal transplants in children. Transplant Proc 1:262-266, Mar 1969
6. Potter D, Belzer FO, Rames L, et al: The treatment of chronic uremia in childhood I.—Transplantation. Pediatrics 45: 432-443, Mar 1970
7. Fine RN, Korsch BM, Stiles Q, et al: Renal transplantation in children. J Pediatr 76:347-357, Mar 1970
8. Gonzales LL, Martin L, West CD, et al: Renal transplantation in children. Arch Surg 101:232-240, Aug 1970
9. LaPlante MP, Kaufmann JJ, Goldman R, et al: Kidney transplantation in children. Pediatrics 46:665-667, Nov 1970
10. Lilly JR, Giles G, Hurwitz R, et al: Renal homotransplantation in pediatric patients. Pediatrics 47:548-557, Mar 1971
11. Lawson RK, Campbell RA, Hodges CV: Renal transplantation in infants and small children. Transplant Proc 3:358-360, Mar 1971
12. Boulten Jones JM, Cameron JS, Berwick M, et al: Treatment of terminal renal failure in children by home dialysis and transplantation. Arch Dis Child 46:457-464, Aug 1971
13. Hulme B, Kenyon JR, Owen K, et al: Renal transplantation in children—Analysis of 25 consecutive transplants in 19 recipients. Arch Dis Child 47:486-494, Aug 1972
14. Advisory Committee to the Renal Transplant Registry: The eleventh report of the Human Renal Transplant Registry. JAMA 226:1197-1204, Dec 3, 1973
15. Reeve CE, Martin DC, Conick HC, et al: Kidney transplantation—A comparison of results using cadaver and related living donors. Am J Med 47:410-420, Sep 1969
16. Cameron JS: The treatment of chronic renal failure in children by regular dialysis and transplantation. Nephron 11:No. 2-4, 221-251, 1973
17. Gruskin CM, Fine RN: Growth in children following renal transplantation. Am J Dis Child 125:514-516, Apr 1973
18. McEnery PT, Gonzales LL, Martin LW, et al: Growth and development of children with renal transplants—Use of alternate-day therapy. J Pediatr 83:806-814, Nov 1973
19. Cerilli J, Evans WE, Sotos JF: Renal transplantation in infants and children. Transplant Proc 4:633-636, Dec 1972

Refer to: Guilleminault C, Eldridge FL, Simmon FB, et al: Sleep apnea syndrome—Can it induce hemodynamic changes? West J Med 123:7-16, Jul 1975

Sleep Apnea Syndrome

Can It Induce Hemodynamic Changes?

CHRISTIAN GUILLEMINAULT, MD, *Stanford,*
FREDERIC L. ELDRIDGE, MD, *Chapel Hill, North Carolina,*
F. BLAIR SIMMON, MD, *and* WILLIAM C. DEMENT, MD, *Stanford*

Of 250 patients referred to the Stanford Sleep Disorders Clinic, 35 were diagnosed for a sleep induced apnea syndrome. Thirty of them (27 adults and 3 children) were nonobese and complained of a sleep disorder. In 12 patients (9 adults and 3 children) extensive cardiorespiratory workups were done during sleep and wakefulness. Three types of sleep induced apnea syndrome were identified: diaphragmatic (or central), obstructive and mixed. The diaphragmatic type was predominant in sleep apnea insomnia; obstructive was predominant in sleep apnea hypersomnia. Hemodynamic changes were documented during sleep. Tracheostomy, done in two cases, improved the sleep induced symptomatology.

In 1956 Burwell and co-workers[1] coined the term "Pickwickian" to describe the cardiorespiratory syndrome of obesity. Extensive studies have since been made on the cardiorespiratory dysfunctions in these patients. In 1969 Lugaresi and co-workers[2] reported the findings from a detailed clinical investigation of a *nonobese* hypersomniac patient and showed that the same sleep related respiratory abnormalities previously reported only in Pickwickian patients were present. In 1970, Coccagna and co-workers[3] postulated the existence of a more general "hypersomnia-hyperventilation syndrome" based on a review of the literature and their own case material. They pointed out that patients classified as Pickwickian, Ondine's Curse[4] or "hypersomnia with periodic respiration"[2] presented three common findings: (a) daytime hypersomnolence, (b) respiratory abnormalities during sleep and (c) hypotonia of the nasopharyngeal muscles during sleep. More recently, respiratory abnormalities during sleep have also been described in nonobese patients classified as rapid eye movement (REM) narcoleptics and insomniacs.[5,6]

From the Sleep Disorders Clinic, Stanford University School of Medicine (Drs. Guilleminault and Dement); the Department of Physiology, University of North Carolina School of Medicine, Chapel Hill (Dr. Eldridge); and the Department of Otolaryngology, Stanford University School of Medicine (Dr. Simmon).

Submitted April 18, 1975.

This research was supported by National Institutes of Neurological Disease and Stroke Grant NS 10727; Research Scientist Development Award MH 05804 (Dr. Dement); Public Health Services Grant NS 09390; and Public Health Service Research Grant N. R.R.-70 from the General Clinical Research Centers, Division of Research Resources.

Information and reprint requests should be addressed to: C. Guilleminault, MD, Sleep Disorders Clinic and Laboratory, Stanford University School of Medicine, Stanford, CA 94305.

ABBREVIATIONS USED IN TEXT

EEG = electroencephalogram
EKG = electrocardiogram
EMG = electromyogram
EOG = electro-oculogram
NREM = nonrapid eye movement
PAP = pulmonary arterial pressure
REM = rapid eye movement

The purpose of the present paper is to report clinical studies that confirm and extend these observations. The occurrence of sleep-related, repetitive apneic episodes in a large case series of nonobese patients who initially were known to complain only of a sleep problem will be reported. In addition, respiratory and pulmonary arterial pressure (PAP) abnormalities during sleep and wakefulness in a subsample of this population will be emphasized.

Methods

Case Finding Techniques

A total of 250 consecutive patients referred to the Stanford Sleep Disorders Clinic underwent continuous polygraphic recording, including respiratory variables, for at least one full night. In all cases, the patients were fully awake at the beginning of the study and had a period of wakefulness in the morning before the tests were terminated. In addition, many had spontaneous periods of wakefulness of varying lengths in the middle of the night.

The polygraphic variables related to monitoring states of sleep and wakefulness were exactly the same in all patients.[7] The electroencephalogram (EEG) was always recorded from the standard C_3/A_2 or symmetrical C_4/A_1 placements of the International 10-20 System.[7] The electro-oculogram (EOG) was recorded either bipolarly from electrodes at the right and left outer canthi, or monopolarly with each canthus referred to the opposite ear lobe. Two closely approximated submental electrodes recorded the digastric electromyogram (EMG). Each successive 30 seconds of polygraphic recording was assigned to a specific category of sleep and wakefulness according to rules and definitions set forth in an internationally recognized standard sleep stage scoring manual.[7]

Four polygraphic tracings were routinely devoted to respiration using thoracic and abdominal mercury strain gauges and buccal and nasal thermistors. This simple respiratory technique does not interfere with the sleep of patients and, at the same time, gives an adequate differentiation between those patients with normal respiration and those whose respiration during sleep is pathological. The polygraphic data from patients were compared with published data on respiration during sleep in normal adults[8-10] and with recordings made on our own normal control groups (5 young adults and 12 older persons ranging from 40 to 60 years of age). The comparisons indicated that the above technique for recording respiration during sleep and wakefulness was an accurate and reliable case finding procedure.

The 250 patients fell almost entirely into three groups: patients complaining of insomnia, patients complaining of daytime sleepiness and long nocturnal sleep times (hypersomnia), and patients who complained of daytime sleep attacks associated with disrupted nocturnal sleep. REM narcolepsy was by far the most prevalent condition in the latter group. All ages were represented, with a peak in the range of 40 to 60 years old. Except for obese patients, sleep related respiratory abnormalities were not usually suspected by the referring physician, the patient or the staff of the Stanford Sleep Disorders Clinic.

Experimental Protocol

When positive findings were obtained in the case finding study, the patient was encouraged to participate in additional evaluations. Thus, in a subsample of the case series, very extensive hemodynamic and pulmonary data were gathered. The size of this subsample (12 patients) was severely limited by many factors. Among them were the availability of testing facilities, the willingness of the patients to undergo additional tests and their ability to be available on the required dates and, finally, a variety of constraints imposed by considerations involving use of human subjects.

Using the simple recording technique described previously, two all-night recordings first were made for each patient in the subsample to confirm sleep pathology and respiration problems during sleep. In patients with complaint of excessive daytime sleep (hypersomniacs or REM narcoleptics) during this two-day period, one 24-hour continuous recording was made to determine the number of sleep attacks during the daytime and to evaluate the severity of the daytime sleepiness. Respiration was also recorded during daytime naps throughout this 24-hour period.

Evaluation during wakefulness. Following this

initial two-day assessment period, all patients followed a four-day 24-hour protocol. During the day, patients were given pulmonary function tests *during wakefulness* that included spirometric tests; studies of lung volume, elastic recoil, air flow resistance and arterial blood gases, and an exercise study which compared rest and three grades of exercise. Also CO_2 response curve and posthyperventilation breathing tests as described by Plum[11] were done. We made certain that patients were awake during respiratory evaluations, although it was often a problem in hypersomniacs. In addition, all patients in the subsample were given careful laryngologic examinations to determine that there was no evident obstruction of the upper airway.

On the last day of the evaluation, cardiac catheterization was carried out in all patients except children. In each adult patient, a catheter was placed in the brachial artery, and a Swan-Ganz catheter was positioned in the pulmonary artery. Continuous recording of pulmonary arterial pressure was made during the subsequent 14 hours which included substantial periods of both wakefulness (in a resting position) and sleep. Arterial blood samples were drawn at various strategic moments throughout the procedure.

Evaluation during sleep. During the first two experimental nights standard sleep measurements were recorded. Respiration was recorded using strain gauges and thermistors, and 200 micron wire electrodes were inserted in intercostal muscles for analysis of EMG during respiratory movements and apneic episodes.

In each patient, on the third and fourth nights, a catheter tip pressure transducer was positioned in the esophagus to record endoesophageal pressure. Peripheral air flow was analyzed using buccal and nasal thermistors as well as a carbon dioxide (CO_2) pickup placed in the oropharynx. The CO_2 pickup measured the percentage of carbon dioxide in the expired air flow. An ear oxymeter continuously measured arterial oxygen saturation. During night four, using the brachioarterial catheter, arterial blood samples were drawn throughout the night for independent validation and calibration of the ear oxymeter.

Definition of Pathological Apneas

An apnea was specifically defined as a cessation of air flow at nose and mouth enduring for a *mininum* of 10 seconds. Apneic events shorter than ten seconds were ignored. An abnormal sleep apnea syndrome was diagnosed if a patient showed a minimum of 30 apneic episodes during seven hours of nocturnal sleep. In addition, the apneic episodes had to occur in nonrapid eye movement (NREM) sleep as well as in REM sleep, and some of the episodes that occurred during NREM periods had to appear in a repetitive sequence. Apneic episodes seen at the onset of sleep or occurring simultaneously with a burst of rapid eye movement are not pathologic.[12]

Three types of apnea have been defined using strain gauge and thermistor recordings made mainly in Pickwickian patients.[13] Specific definitions of types of apnea used in our clinical investigations were consonant with previous guidelines. *Central apnea* was defined by the absence of airflow (indicated by a flat tracing in *both* nasal and buccal thermistors) accompanied by absence of respiratory efforts (indicated by flat tracings in the abdominal and thoracic strain gauges). An esophageal pressure transducer gave a somewhat more reliable recording of respiratory effort, and the cessation of air exchange was confirmed by an ear oxymeter. *Obstructive or upper airway* apnea* was defined for intervals of ten seconds or longer during which there was an absence of airflow (determined by flat tracings in both nasal and buccal thermistors) while the thoracic and abdominal strain gauges showed persistent respiratory effort. Once again, if in place, the esophageal pressure transducer gave a clearer measure of respiratory effort. When micro-wire needle electrodes were inserted in the intercostal muscles, they showed a cessation of intercostal activity during a central apnea; during an upper airway apnea, they generally showed a persistent rhythmic activity which tended to increase in intensity as the apnea progressed. A *mixed or complex apnea* was defined for all intervals of ten seconds or longer during which there was a complete cessation of airflow accompanied by an absence of respiratory effort in the early part of the apneic episode and a resumption of respiratory effort in the latter part. In other words, a mixed apnea had the appearance of a central apnea giving way to an upper airway apnea. The reverse order never seemed to occur.

Two sources of artifact were troublesome. First, prolonged upper airway apnea was accompanied

*We prefer the term "upper airway" apnea, to the widely used "obstructive" apnea. The latter has the unfortunate connotation of a physical obstruction to many, such as intrathoracic goiter, tracheal constriction and the like. These physical obstructions would also be present during wakefulness whereas the functional apneas under consideration appear to be present only during sleep.

by increasing respiratory effort with recruitment of accessory mechanisms that frequently led to fairly vigorous rhythmic body movement. This movement, in turn, often produced artifactual rhythmic deflections on the thermistors tracings. Second, the mercury strain gauges around thorax and abdomen occasionally went out of adjustment leading to an artifactually flat tracing. As indicated earlier, patients were recorded at least one night with intraesophageal pressure transducer and ear oxymeter which greatly increased the reliability of the respiratory evaluation.

Results

General Observations

On the basis of all-night polygraphic recordings, 35 of the 250 patients referred for evaluation of a sleep disorder complaint were diagnosed as having an abnormal sleep apnea syndrome. In nearly every case, the sleep related apneic condition was unambiguously pathological, well beyond the previously stated criteria. Repetitive episodes were seen in NREM sleep and hundreds of individual apneas were tabulated. In every one of the 35 cases, apneic episodes were present only during sleep; spontaneous or induced awakenings were always associated with the resumption of normal respiration. In particular, the fairly lengthy periods of polygraphic wakefulness at the beginning and end of the all-night recording sessions were characteristically associated with rhythmic breathing.

Although the gender of the total patient population was equally distributed, only one of the 35 sleep apnea patients was female. Thirty of the 35 were *not* obese (normal statistical values corrected for height and age were used[14] and the diagnosis of obesity was applied only to patients who were more than 25 percent overweight). Interestingly enough, the proportion of obese patients was slightly higher in the 215 patients who had normal respiration during sleep. The ages of the 35 sleep apnea patients ranged from 9 to 70, with the majority in their forties and fifties. Ten were initially referred with the complaint of insomnia, 14 with uncomplicated daytime sleepiness, and 11 were classified by us as REM narcoleptics.

An important observation was that 16 of the nonobese sleep apnea patients had a moderate essential hypertension and 3 of the 16 had some EKG abnormalities.

Experimental Protocol

Twelve patients were available for further studies. In addition to the previously mentioned factors that influenced their ability to participate, an attempt was made to restrict the subsample to patients who did not have any cardiac abnormality or hypertension during the daytime when first seen in the Sleep Disorders Clinic. The exclusion criteria were not rigid, however, and the final sample included one patient with abnormal findings on an electrocardiogram (EKG) and one with moderate hypertension.

None of the 12 patients was obese. Three were children aged 9, 11 and 15 years. The latter was the only female in the entire group. All three children were enuretics. One of the 12 was 70 years old and the remaining 8 ranged from 35 to 59 years old (mean = 48 years). Two patients complained of insomnia, 5 presented REM narcolepsy, and 5 patients, including the 3 children, presented hypersomnia.

Because of the previously mentioned artifacts, we will present quantitative data only from these 12 patients.

Clinical symptomatology. Although none of the patients in the subsample was either aware of or complained of any respiratory problem, we learned from the patients' spouses (or mothers in the three children) that the patients were very loud snorers, and that the history of snoring had always preceded the sleep complaint. Several patients were also described as having a snorting or gasping respiration during sleep. The shortest interval reported between the onset of snoring and the onset of a sleep complaint was two years. Polygraphic recordings confirmed that snoring occurred as patients began to breathe at the end of each apneic episode.

Sleep pathology and sleep recordings. The polygraphic recordings confirmed the clinical diagnosis of insomnia, REM narcolepsy, and hypersomnia in the respective patients. An abnormal sleep structure was also present in each case; despite the three different clinical complaints, a great reduction or a complete absence of stage 3 and 4 NREM (slow wave) sleep occurred in all 12 patients. The definition of sleep stages was difficult in patients presenting predominantly obstructive apnea, since the resumption of respiration was usually accompanied by snorting and movement artifact which

made the polygraphic recordings difficult to evaluate. All of the patients, even those complaining of insomnia, were difficult to awaken during the apneic episodes, and, if suddenly awakened, were completely disoriented and unable to cope with the surrounding reality. Their sleep was very agitated, and frequently these patients presented abnormal movements before resuming respiration at the end of apnea. These movements were either simple movements of the feet and hands, best described as a "flapping tremor," or were of a greater magnitude involving the whole body. (Fifteen minutes after sleep onset the bed usually looked like a battlefield.)

The fewest apneic episodes recorded on a single night was 68 and the most was 682. Apnea ranged in duration from 10 to 190 seconds. However, each of the categories of sleep disorders differed slightly in the mean duration of an apnea: insomniacs on the average having the longest apneic episodes (mean = 44 seconds) and REM narcoleptics having the shortest (mean = 19 seconds). The duration of apneic episodes varied widely in each patient. No explanation for the continuous intrasubject variations as yet has been found. The three types of sleep disorders also differed in the type of predominant apnea they presented; though all three types of apnea were seen in all cases, central apnea was predominant in insomniacs while the predominant apnea for hypersomniacs and REM narcoleptics was obstructive (see Table 1).

Hypersomniacs, REM narcoleptics and insomniacs behaved differently at the end of an apneic episode. When hypersomniac patients resumed breathing, the EEG usually changed from a theta rhythm to a slow alpha which looked like stage 1 NREM sleep. However, sleep stages were difficult to identify in these recordings since the apneas were predominantly obstructive and caused artifact in the recordings. Hypersomniac patients seldom presented short alpha arousals at the end of an apneic episode. The digastric EMG, which during the episode was very low and similar to that of REM sleep, suddenly increased at the end of the apneic episode.

In the REM narcoleptics, who also presented predominantly obstructive apneas, the sleep recordings were similar to those of the hypersomniacs. However, the former more frequently presented short alpha arousals (arousals with alpha rhythm in the EEG) than did the hypersomniacs. In addition, longer awakenings which are part of the classical symptom of disrupted nocturnal sleep in REM narcolepsy more frequently followed the end of an apneic episode in REM narcoleptics than in hypersomniacs.

Since the insomniacs presented predominantly nonobstructive apneas, sleep stages were more easily identified in their recordings than in those of the hypersomniacs and REM narcoleptics. Of the three sleep disorders, insomniacs most frequently presented alpha arousals at the end of an apneic episode. However, occasionally only a lightening of sleep, a change from NREM stage 2 to stage 1, rather than a complete arousal occurred. For reasons that we have been unable to determine, after repetitive apneic episodes insomniac patients awakened completely. Neither the number of previous apneic episodes nor the duration of any given apneic episode appeared to be related to the awakenings. The patients stayed awake for 10 to 60 minutes and presented three to six such waking periods per recording night.

Blood gas values during sleep. Blood gas values showed extreme fluctuations during the repetitive sleep apneic episodes. Oxygen levels reached high values of 96 mm of mercury following resumption of respiration and fell as low as 40 mm of mercury at the end of an apneic episode. Concurrently measured carbon dioxide pressure (PCO_2) ranged from levels near 40 mm of mercury up to 60 mm of mercury during the longest apnea. Most of the data were from the nine adults. In the three chil-

TABLE 1.—*Types of Apnea Presented by the Patients Studied*

Patient Population	*Mean total of apneic episodes per night*	*Mean duration of each apnea (seconds)*	*Mean percent of apnea occurring during NREM sleep*	*Type of predominant apnea as percent of total apneas**
Insomniac, N=2	236	44.0	87.5	Diaphragmatic (central) 95.0
Hypersomniacs, N=5	474	31.3	88.5	Obstructive 85.4
REM narcoleptics, N=5	220	19.0	93.2	Obstructive 49.2

*Though all three types of apnea (diaphragmatic [central], obstructive and mixed) were seen, values are given only for the *predominant* type of apnea observed in each classification.

dren, the brachio-arterial catheter was not left overnight, but samples were drawn during wakefulness and one daytime nap.

Pulmonary arterial pressure during sleep. Throughout the night, in association with the repetitive apneic episodes, a progressive increase in systolic and diastolic pulmonary arterial pressure was recorded. Pulmonary arterial pressure reached levels as high as 87 mm of mercury (systolic) and 50 mm of mercury (diastolic). The patients who had primarily diaphragmatic (central) apneic episodes showed less severe increases in

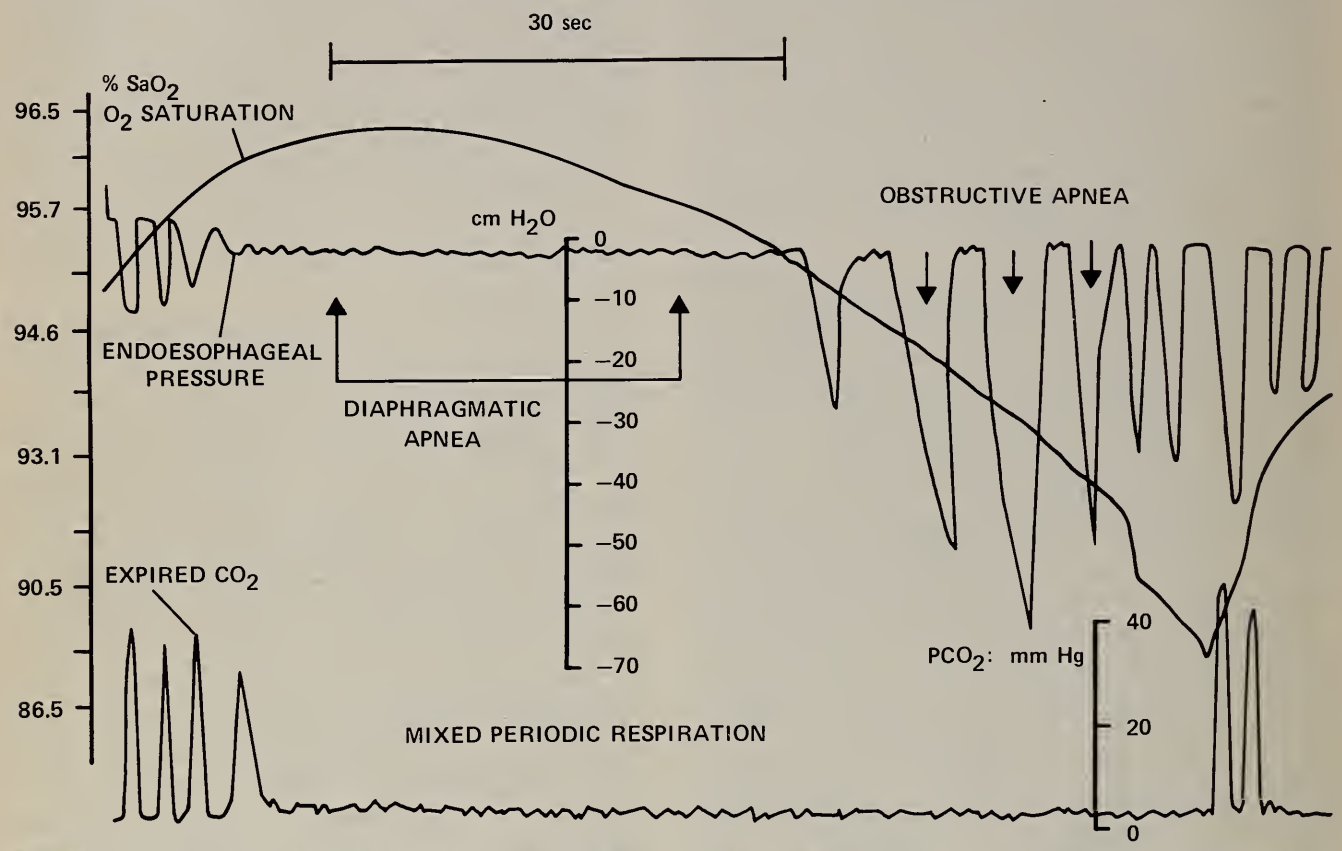


Figure 1.—Polygraphic recording of a mixed type sleep apnea in a 49-year old man whose daytime pulmonary function tests are reported in Table 2. At the beginning of the record there is a "stopped diaphragm" episode; then, on the right half of the recording, one can see that diaphragmatic movements resume (endo-esophageal pressure), but no air flows at the peripheral level. The endo-esophageal pressure progressively increases until, finally, the peripheral obstruction is lifted and air flows normally through nose and mouth.

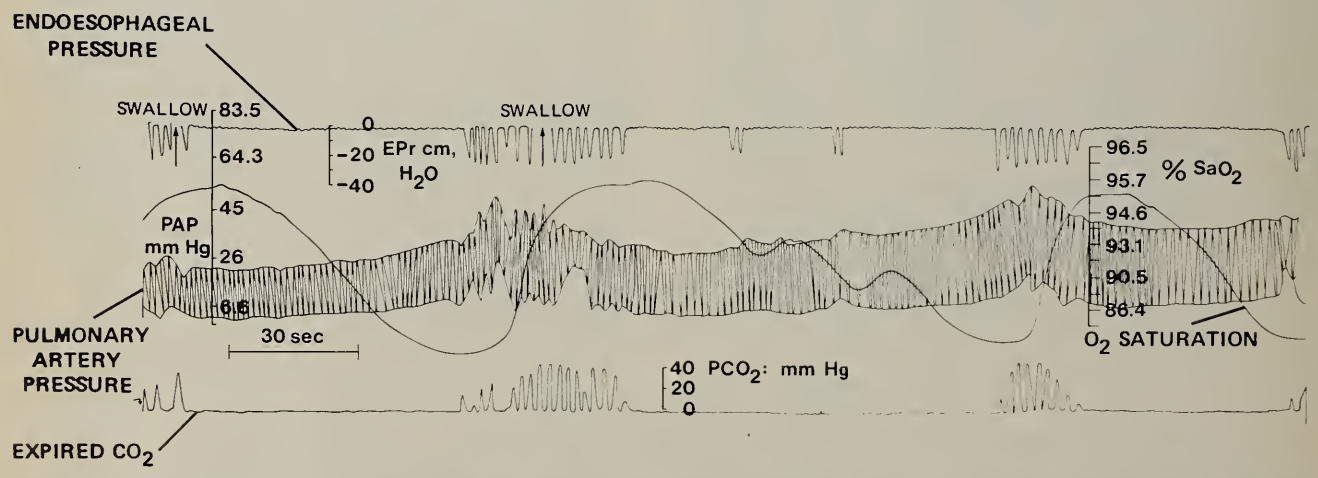


Figure 2.—Recording during sleep of a 54-year-old man who presents repetitive diaphragmatic apneic episodes. In each of the three episodes shown, pulmonary arterial pressure gradually increased during the episodes reaching a peak at the resumption of ventilation. These episodes occurred at the beginning of a series of repetitive apneic episodes; in less than ten minutes, the pulmonary arterial pressure reached values as high as 62 mm of mercury (systolic) and 45 mm of mercury (diastolic) at the end of a sleep apneic episode.

pulmonary arterial pressure than those with predominantly obstructive apnea.

The systolic and diastolic pulmonary arterial pressure usually began to increase after 15 to 20 seconds of apnea. In isolated apneic episodes, the pulmonary arterial pressure returned to the baseline level when normal respiration resumed. When several consecutive apneic episodes occurred, the systolic and diastolic pulmonary arterial pressure did not return to baseline levels between apneic episodes, but progressively rose to the highest values after five to ten minutes of repetitive apnea. When a normal breathing pattern was resumed or if the patient was awakened, the pulmonary arterial pressure returned to normal values in less than 100 seconds.

The highest systolic and diastolic pulmonary arterial values were always recorded at the resumption of respiration, between two consecutive apneic episodes. The systolic and diastolic pulmonary arterial pressure values were higher when associated with repetitive obstructive apneas than with diaphragmatic (central) apneas. This relationship was present even if the duration of the apnea was similar and even if the blood gas measurements showed a similar degree of hypoxemia, hypercapnia and acidosis.

Pulmonary studies during wakefulness. The waking pulmonary evaluations of the sleep apneic patients were compared to results obtained in the same laboratory on normals and patients with chronic lung diseases. Daytime pulmonary studies made both at rest and during exercise were within normal limits (see Table 2) in all sleep apneic patients. The waking oxygen saturation levels were also normal or slightly below normal in all patients (the lowest value was 94 percent oxygen saturation in one hypersomniac patient). The post-hyperventilation test was normal except for the 9-year-old child who showed considerably greater hypoventilation than his resting baseline level.

The CO_2 response curve was the only test for which results were below normal levels in two adults and the 9-year-old child. The two adults presented a slower rate of increase than normal (with 14 and 14.5 liters per minute for 48 mm of mercury compared with 21 to 23 liters per minute for controls) and reached a plateau with ventilation of 25 liters per minute at 50 mm of mercury. These results are borderline normal. In the 9-

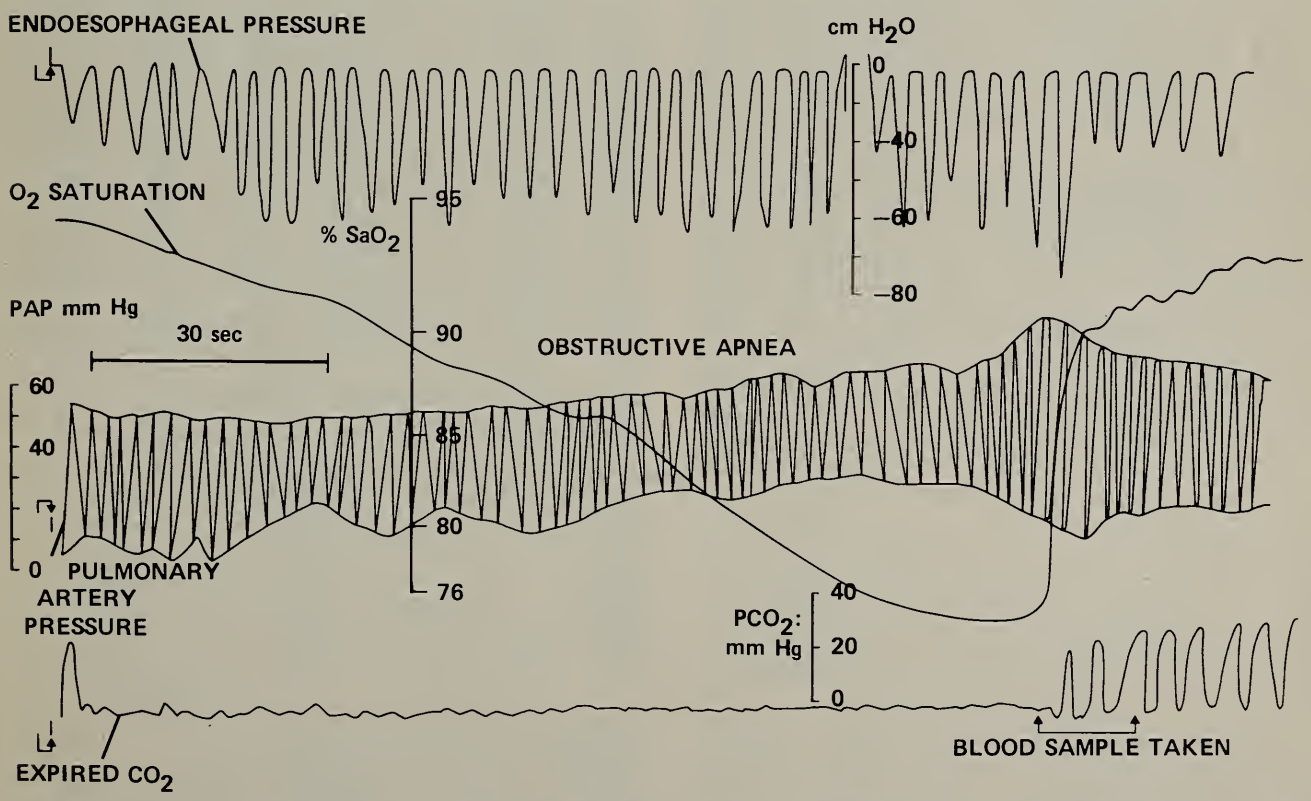


Figure 3.—Recording of an obstructive sleep apneic episode of 165 seconds duration in a 48-year-old man. The pulmonary arterial pressure progressively increased and was 75 mm of mercury (systolic) and 25 mm of mercury (diastolic) at the end of the episode when respiration resumed through the upper airway (airway PCO_2). When the blood sample was drawn, the following values were obtained: pH=7.28; arterial carbon dioxide partial pressure ($PaCO_2$)=47 mm of mercury; arterial oxygen partial pressure (PaO_2)=46 mm of mercury; arterial oxygen saturation (SaO_2)=71.5 percent.

year-old boy the CO_2 response curve was significantly lower than normal value.

Rhinolaryngologic examination during wakefulness. Laryngologic examination of patients with predominantly obstructive sleep apnea failed to show any defect responsible for the functional obstruction during sleep.

Follow-up and treatment. Four hypersomniac patients (two adults and two children) with predominantly obstructive sleep apnea syndromes were monitored for one night with a rigid hypopharyngeal tube positioned through the nostril. For three patients this procedure did not decrease the number of obstructive apneas during sleep compared with results of previous recordings. In the fourth case there was a 10 percent decrease from baseline. One adult hypersomniac patient had nasal reconstruction, but the number of apneic episodes remained unchanged.

During the follow-up period the sleep disorder increasingly impaired the daily lives of the 12- and 15-year-old children. In the 12-year-old child, an adenoidectomy and a tonsillectomy were done during the follow-up period with no improvement of the apnea syndrome. In both children, a borderline but progressive hypertension developed (blood pressure = 150/100 and 160/105 mm of mercury). No specific cause could be found to explain the development of this symptom in spite of an extensive evaluation. A chronic tracheostomy was then carried out on both children. Within 15 hours after the procedure the systemic hyperten-

TABLE 2.—*Results of Daytime Pulmonary Studies in a Patient with Predominant Central Apneic Episodes (Patient 1) and in a Patient with Mixed and Obstructive Apnea (Patient 2)*

	Patient 1—54-year-old man					*Patient 2—49-year-old man*			
		Exercise Sessions					*Exercise Sessions*		
	Supine Rest	*No. 1*	*No. 2*	*No. 3*	*No. 4*	*Supine Rest*	*No. 1*	*No. 2*	*No. 3*
Bicycle ergometer	0	300	600	900	1,100	..	300	600	900
Heart rate	53	58	95	135	170	86	106	134	172
Arterial PO_2 (mmHg)	97	98	100	93	97	95	94	90	93
Arterial PCO_2 (mmHg)	34	42	42	41	35	40	45	46	41
Arterial pH	7.44	7.35	7.35	7.33	7.30	7.35	7.33	7.30	7.26
Arterial HCO_3 (mEq/L)	22.5	22.5	22.5	21.0	16.7	21.5	23	21.9	17.8
Arterial O_2 sat. (percent)	97.2	97.5	97.2	96.0	96.0	94.6	95.6	95.3	95.2
Resp. rate (freq/min)	20.7	20.5	23.5	28.0	33.0	13.7	19.5	23	27.5
Tidal volume (ml)	632	1,167	1,660	2,130	2,574	474	968	1,393	1,708
Minute ventilation	13.1	23.9	39.0	59.6	84.9	6.5	18.9	32.0	47.0
Alveolar ventilation	8.36	15.6	28.8	40.8	63.2	4.6	12.5	23.1	38.9
Dead space ventilation	4.71	8.28	10.2	18.9	21.8	1.9	6.4	8.9	8.1
Dead space/tidal vol. (percent)	36.0	34.6	26.0	31.6	25.6	28.6	33.7	27.8	17.2
O_2 uptake (L/min)	0.34	0.92	1.55	2.19	2.73	.223	.787	1.432	1.956
O_2 uptake index	4.8	13.2	22.2	31.2	39	3.36	11.9	21.6	25.5
O_2 pulse max.	0.09	0.23	0.23	0.23	0.23	..	..	..	..
Alveolar PO_2 (mmHg)	115	110	104	104	112	107.5	96.3	96.8	105.7
Alveolar-arterial O_2 diff. (mmHg)	18	2	4	11	15	12.5	2.3	6.8	12.7
CO_2 production (L/min)	.329	.760	1.40	1.94	2.56	..	..	..	..
Resp. exchange ratio	.98	.82	.90	.88	.935	.97	.83	.86	.95
Vent. equiv. O_2 uptake	38.9	25.9	25.1	27.1	31.0	..	..	..	..

	Lung Volumes	*Predicted Normal*	*Lung Volumes*	*Predicted Normal*
Vital capacity (cc)	4774	4320	3434	3690
Insp. capacity (cc)	2980	2880	2203	2460
Exp. reserve vol. (cc)	1794	1440	1231	1230
FRC (cc)	4280	3408	2888	2796
Residual vol. (cc)	2486	1968	1657	1566
Total lung capacity (cc)	7260	6288	5091	5256
Helium wash-out (min)	20	Stabilized at 18	20	Stabilized at 10 and 19

Ventilatory Mechanics	*Pre-*	*Post-*	*Predicted Normal*	*Pre-*	*Post-*	*Predicted Normal*
Timed exp. capacity (cc)	4573	4396	4320	3173	3173	3690
in seconds	9	11	..	5.2	3.7	..
Max exp. flow rate, L/min.	360	281	223	423	466	262
Max. breathing cap., L/min.	154	176	142	134	156	131

Resp. = respiration
freq/min = frequency/minute
Vol. = volume
Max. = maximum
Vent. equiv = ventilatory equivalent
insp. = inspiratory
exp. = expiratory
FRC = functional respiratory capacity
Cap. = capacity
Sat. = saturated

sion was no longer present (blood pressure = 120/80 and 125/80 mm of mercury). Episodes of sleep apnea were also virtually eliminated after tracheostomy.

Comment

The occurrence of minor respiratory irregularities in normal adults during sleep is well known.[13-16] Sudden death during sleep has been reported in patients with neurological problems involving respiratory areas,[17,18] such as poliomyelitis and Ondine's Curse syndrome. The typical Pickwickian syndrome, where respiratory and cardiovascular dysfunctions during both sleep and wakefulness are associated with obesity, has been well documented.

The present study indicates that respiratory abnormalities, which previously had been emphasized only in populations with obvious central nervous system pathology or in notably obese populations, are also found rather commonly during the sleep of nonobese patients who have a chronic sleep disturbance. Indeed, the present case finding data from male sleep disorder patients suggest that the frequency of a sleep apnea syndrome among such patients may be as high as 25 to 30 percent. It should also be emphasized that with rare exceptions, absolutely no abnormality existed in the waking state. Thus examinations conducted during wakefulness would clearly fail to show any problem. This factor explains why the condition remained uniformly undiscovered at the time of referral in our case series, and further dictates that all male patients complaining of a sleep problem should routinely have respiratory evaluation during sleep. Although none of the patients was specifically aware of the respiratory problem, a history of heavy snoring, beginning before the development of the sleep disorder, was present in every case. Such a history should probably be regarded as an important diagnostic clue.

All of the patients in this study—insomniacs, REM narcoleptics and hypersomniacs—although nonobese, presented patterns during sleep similar to those seen in obese Pickwickian patients. The rate of respiratory pauses during sleep was the same as that occurring in the Pickwickian syndrome, and a similar degree of hypoxemia, hypercapnia and acidosis occurred repetitively throughout the night in association with these pauses. Changes in pulmonary arterial pressure during sleep were also similar to those reported by Coccagna and co-workers,[19] Lonsdorfer and co-workers,[20] Kurtz and co-workers[21] and Fruhman[17] in Pickwickian patients and in patients having a primary hypoventilation syndrome. However, unlike both the Pickwickian patients and the patients with primary hypoventilation syndromes (except for one child with an abnormal CO_2 response curve and an abnormal posthyperventilation test), the nonobese patients in the present study had normal pulmonary function during wakefulness.

What leads to a respiratory abnormality during sleep in these patients? Since no primary defect in the respiratory control mechanisms was detected during wakefulness, the abnormality in breathing would appear to be related to central nervous system structures involving both brain-stem respiratory neurons and neurons controlling sleep.

A second question is: Why do each of these apneic episodes end? The carotid chemoreceptors could be involved in the sudden resumption of respiration, particularly in diaphragmatic (central) apnea, but it is difficult to understand why the durations of apneic episodes have wide variations in individual patients. One would assume that, if hypoxemia, hypercapnia and acidosis played a major role in the resumption of respiration, an apneic episode would end when specific low values were reached. This was not the case; some apneic episodes were very short, the episode ending before significant changes occurred in the blood gas levels.

A relationship was found between the three different sleep disorders and the type of sleep induced respiratory abnormality; while all three types of apnea were observed, sleep apneic patients with insomnia presented a predominance of diaphragmatic (central) type apnea, and REM narcoleptics and hypersomniacs with sleep apnea had a majority of obstructive pauses. The sample sizes for these three categories of sleep disorders were small, but further experience with a larger number of sleep apneic insomniacs, REM narcoleptics and hypersomniacs has confirmed this relationship. One hypothesis suggested by this relationship is that the difference in the type of predominant apnea could account for the difference in the sleep symptomatology. Although these patients differed in both the type of sleep complaint and the type of predominant apnea, the pulmonary arterial changes during sleep and the frequency of systemic hypertension during wakefulness were similar in the two groups.

An "essential" hypertension was found in approximately half of the nonobese apneic patients

in this study. Can sleep apnea induce secondary, permanent cardiovascular changes? Although we were unable to continuously monitor the systemic arterial pressure during sleep before and after tracheostomy as did Coccagna and co-workers[22] in five similar cases, we would like to emphasize the medical history of the two children. After a tracheostomy, which bypassed the functional obstruction induced by sleep, the essential hypertension disappeared completely. It is difficult to determine exactly why systemic arterial pressure may be influenced by sleep apneic episodes. Our current hypothesis is that repetitive hypoxia, hypercapnia and acidosis are involved. We are currently testing this hypothesis using a more extensive cardiovascular protocol and a new series of sleep apneic patients.

A final issue is the possible interaction of certain drugs which depress the central nervous system control of respiration with the sleep apneic syndrome. At least two instances of barbiturate-induced crises have already been reported in patients with sleep apnea; one eventually led to death.[23] One of our obstructive sleep apneic patients had an acute respiratory episode with upper airway obstruction secondary to a supposed hypopharyngeal collapse. This episode was precipitated by 10 mg intramuscular injections of diazepam given twice at one-hour intervals as a premedication for surgical operation. Within 10 minutes after the second injection, the patient presented such a severe reaction that an emergency tracheostomy was considered. These reactions suggest that certain chemotherapies should be cautiously applied to patients who may have a sleep apnea syndrome, especially since physicians frequently prescribe barbiturates or benzodiazepines or both for insomniacs.

After this report was submitted, we became aware of a paper by Sackner and co-workers[24] describing the existence of a typical sleep apnea syndrome in 12 adult patients presenting with daytime sleepiness. In their case material, only two patients fail to meet the 25 percent overweight criterion of obesity. Their data therefore suggest a need for increased awareness of the existence of these problems in the nonobese population.

REFERENCES

1. Burwell C, Robin E, Whaley R, et al: Extreme obesity associated with alveolar hypoventilation: A Pickwickian syndrome. Am J Med 21:811-818, 1956
2. Lugaresi E, Coccagna G, Mantovani M, et al: Impersonnie essenziali associate a respirazione periodica. Sist Nerv 21:18-27, 1969
3. Coccagna G, Mantovani M, Berti-Ceroni G, et al: Sindromi ipersonniche-ipoventilatore. Minn Med 61:1073-1084, 1970
4. Severinghaus J, Mitchell R: Ondine's curse—Failure of respiratory center automatically while awake. Clin Res 10:122, 1962
5. Guilleminault C, Eldridge F, Dement W: Narcolepsy, insomnia and sleep apneas. Bull Physiopathol Resp 8:1127-1138, 1972
6. Guilleminault C, Eldridge F, Dement W: Insomnia with sleep apnea—A new syndrome. Science 181:856-858, 1973
7. Rechtschaffen A, Kales A: Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. National Institutes of Health Publication No. 204. Washington, DC, Superintendent of Documents, Book 1-62, 1968
8. Bulow K, Ingvar D: Respiration and state of wakefulness in normals studied by spyrography, capnography and EEG. Acta Physiol Scand 51:230-238, 1961
9. Duron B, Tassinari C, Gastaut H: Analyse spirographique et electromyographique de la respiration au cours du sommeil controlé per l'EEG chez l'homme normal. Rev Neurol 115:562-574, 1966
10. Duron B: La fonction respiratoire pendant le sommeil physiologique. Bull Physiopathol Resp 8:1277-1288, 1972
11. Plum F, Brown H, Snoep E: Neurologic significance of post-hyperventilation apnea. JAMA 181:1050-1055, 1962
12. Aserinsky E: Physiological activity associated with segments of the rapid eye movement period, *In* Kety S, Evarts E, Williams H (Eds): Sleep and Altered States of Consciousness. Baltimore, Williams and Wilkins, 1967, pp 335-350
13. Tassinari C, Dalla Bernardina B, Cirignotta F: Apneic periods and the respiratory related arousal patterns during sleep in the Pickwickian syndrome: a polygraphic study. Bull Physiopathol Res 8:1087-1102, 1972
14. Weights, Height and Age of Adults—United States, 1960-1962. U.S. Public Health Service. Public Health Service Publication No. 1000, Series U-No. 14: Washington, DC, 1966
15. Snyder F, Hobson J, Morrison D, et al: Changes in respiration, heart rate and systolic blood pressure in human sleep. J Appl Physiol 19:417-422, 1964
16. Robin E, Whaley R, Crump C, et al: Alveolar gas tension, pulmonary ventilation and blood pH during physiologic sleep in normal subjects. J Clin Invest 37:981-989, 1958
17. Fruhman G: Hypersomnia with primary hypoventilation syndrome and following cor pulmonale. Bull Physiopathol Resp 8: 1173-1179, 1972
18. Plum F, Swanson A: Abnormalities in central regulation of respiration in acute and convalescent poliomyelitis. Arch Neurol and Psych 80:267-285, 1958
19. Coccagna G, Mantovani M, Brignami F, et al: Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Physiopathol Resp 8:1159-1172, 1972
20. Lonsdorfer J, Meunier-Carus J, Lampert-Benignus E, et al: Aspects hemodynamiques et respiratoires du syndrome Pickwickien. Bull Physiopathol Resp 8:1181-1192, 1972
21. Kurtz D, Bapst-Reiter J, Fletto R, et al: Les formes de transition du syndrome Pickwickien. Bull Physiopathol Resp 8: 1115-1125, 1972
22. Coccagna G, Mantovani M, Brignami F, et al: Tracheostomy in hypersomnia with periodic breathing. Bull Physiopathol Resp 8:1217-1227, 1972
23. Hishikawa Y, Furuya E, Wakamatsu H, et al: A polygraphic study of hypersomnia with periodic breathing and primary alveolar hypoventilation. Bull Physiopathol Resp 8:1139-1151, 1972
24. Sackner M, Landa J, Forrest T, et al: Periodic sleep apnea —Chronic sleep deprivation related to intermittent upper airway obstruction and central nervous system disturbance. Chest 67: 164-171, 1975

Refer to: Krone LR, Prichard LL, Bradshaw CL, et al: Antenatal diagnosis of an XXX female—A dilemma for genetic counseling. West J Med 123:17-21, Jul 1975

Antenatal Diagnosis of an XXX Female

A Dilemma for Genetic Counseling

LAWRENCE R. KRONE, BS, LORRAINE L. PRICHARD, PHN, CHRISTY L. BRADSHAW, BS, *and* OLIVER W. JONES, MD, *La Jolla,*
RAYMOND M. PETERSON, MD, *and* BARBARA K. DIXSON, RN, MN, *San Diego*

This report describes the first antenatal diagnosis of an XXX female. Over 150 postnatal cases of XXX females have been described. There is no specific phenotype associated with the sex chromosome abnormality and most such persons are fertile. The frequency of XXX females in mental institutions is 3.9 per 1,000 female subjects whereas the frequency in consecutive newborn infants is 1.1 per 1,000 newborns. Chi-square analysis shows this difference cannot be due to chance. On the other hand, data from consecutive newborn studies suggest that intellectual development in XXX newborns is within normal range. Available evidence favors normal development in XXX female infants although the risk for developmental disabilities may be higher for the XXX than for the XX infant.

ANTENATAL DIAGNOSIS of chromosome disorders which are known to result in the birth of infants with serious defects (such as 21-trisomy, 13-trisomy) rarely poses any difficulty in arriving at a decision to support termination of pregnancy. Unexpected karyotype results showing other trisomic autosomes (such as trisomy 9) also pose little difficulty in counseling since the odds overwhelmingly favor a severely defective fetus. In contrast, the decision may be less straightforward or based upon less objective data when one is faced with a prenatal diagnosis of sex chromosome nondisjunction or structural rearrangement. Moreover, since all forms of nondisjunction involving sex chromosomes represent new or initial spontaneous abnormalities and since in virtually all prenatal analysis of fetal karyotypes one is looking for abnormalities in the autosomes, the finding of a sex chromosome variation is usually unanticipated. Often the par-

From the Department of Medicine, Division of Medical Genetics, University of California, San Diego, School of Medicine, La Jolla, and the Regional Center for Developmental Disabilities, Children's Health Center, San Diego.

Submitted, revised, February 6, 1975.

This study was supported in part by a grant from the National Foundation, March of Dimes, and GM17702, a grant from the National Institutes of Health.

Reprint requests to O. W. Jones, MD, Department of Medicine (M-013), University of California, San Diego, La Jolla, CA 92037.

Figure 1.—Fetal karyotype from cultured fetal fibroblasts. Chromosomes were stained with Giemsa and classified according to the 1971 Paris Conference on Standardization in Human Cytogenetics.[1]

ents have not been prepared by prior counseling that sex chromosome abnormalities have much less certainty as to severe handicaps, such as mental retardation. There are limited factual data upon which to advise couples regarding the risks of all birth defects, including mental retardation, in infants with sex chromosome abnormalities.

This report describes the first known antenatal diagnosis of an XXX female fetus and the difficulty in counseling based upon current knowledge of this sex chromosome nondisjunction and associated clinical manifestations.

Report of a Case

The mother is a 39-year-old (gravida 1, para 0, abortions 0) Caucasian who was referred for amniocentesis because of maternal age. At 16 weeks gestation, an uneventful amniocentesis was done. Fifteen milliliters of straw-colored amniotic fluid were obtained, the cells removed and cultured in F-12 media (Grand Island Biological Company) in a 10 percent CO_2 atmosphere. After 2½ weeks of cell growth, the culture was harvested and karyotype analysis was made on cells arrested in metaphase. Of 30 cells examined, all had a 47, XXX pattern (Figure 1). Subsequent culture of the mother's peripheral blood lymphocytes showed a normal 46, XX pattern.

The prospective parents elected to continue the pregnancy after all current knowledge regarding 47, XXX females was discussed with them. The remaining gestational period was uneventful and the infant was delivered at term with no complications. An Apgar score of 9 was recorded at one minute. A neonatal lymphocyte karyotype confirmed the diagnosis of 47, XXX. On neonatal examination, the infant appeared normal and had no physical abnormalities. Measurements included

a weight of 2.8 kg, height of 47.5 cm, head circumference of 33 cm, and chest circumference of 32 cm.

The infant was subsequently examined at age 32 weeks. In general, the infant is thriving and appears healthy at this age. The weight is 7.3 kg (16th percentile for age), height 67.5 cm (25th percentile for age), head circumference 43 cm (33rd percentile for age). Results of complete physical examination and motor developmental milestones are both considered normal at this age. Developmental testing using Gesell Standards showed that at 32 weeks of age the motor development is 32 weeks; adaptive, 28 weeks; language, 28 weeks; and personal-social, 28 weeks—all of which are well within normal limits. Annual developmental evaluation of this child will be continued.

Discussion

Once the antenatal diagnosis of 47, XXX female was established, we were confronted with the problem of what to advise the prospective parents. A major concern was the possibility of an intellectual handicap in this child because of the reported relationship between 47, XXX and mental retardation. However, virtually all published studies of this association are from studies of such females in various mental institutions. In contrast, consultation with several, but by no means an exhaustive list of geneticists throughout the country showed that from personal experience with 47, XXX females, the incidence of mental retardation and other birth defects is low. Moreover, we were influenced by the fact that this was the mother's first pregnancy, one that she wanted very much, and by the fact that the mother was 39 years old. Thus, we supported their wish to continue this pregnancy.

Since Jacobs and co-workers described the first XXX female,[2] over 150 cases have been documented. Much evidence has been reported about a high incidence of mental retardation in XXX females. However, the sampling is biased and this correlation is not clearly established.

No characteristic phenotype has been found in XXX females, unlike other sex chromosome abnormalities, for example, Turner's (XO) syndrome. However, a variety of physical abnormalities has been cited.[2-17] A proportion of XXX females have underdeveloped secondary sex characteristics, occasionally leading to an onset of secondary amenorrhea early in life. The majority display normal sexual development and are fertile. At least 33 children have been borne by 11 such females,[2-17] with only one case of nondisjunction being reported exhibiting 21-trisomy.[14] The mother of this child with Down's syndrome was identified as a phenotypically and mentally normal XXX female. Theoretically, it is expected that half of the births to XXX females would karyotypically display three sex chromosomes. Although four XXY sons and one XXX/XX daughter have been borne to XXX mothers,[18] the large majority of progeny have a normal karyotype. It may be possible that some selective mechanism exists to reduce the stability of the XX gametes.

Of the 152 XXX females described previously, 97 were considered to be mentally retarded. However, a large majority of retarded XXX females were ascertained by surveying mental institutions and hospitals.

In surveys of 8,300 female patients in mental institutions,[19-26] the composite frequency of XXX females is 3.9 per 1,000 female subjects whereas the frequency of XXX females in a large combined consecutive newborn study of 26,000 female infants is 1.1 per 1,000 newborn females.[27-31]

A chi-square analysis involving approximately 26,000 newborn females and 8,300 female patients in institutions gives a value of 29.01. This shows that chance alone could not possibly account for the difference between the XXX frequency found in the studies of patients in institutions and in the consecutive newborn studies. The greater the chi-square value, the less the role that chance plays. These results appear significant. Accepting this, how detrimental, if at all, are the effects of possessing a 47, XXX karotype? What are the chances that an XXX female will be placed in an institution because of mental retardation? These questions are important for a gravida who, through amniocentesis and fetal karyotyping, knows that she is carrying an XXX fetus and seeks advice from a genetic counselor. At present, it may not be possible to give accurate figures for the probability for an XXX female infant to have a developmental disability, either mental or physical. However, one might be able to make a reasonable assessment of the probability that an XXX female will be admitted to an institution. For example, in the state of California there are currently 4,065 females in institutions for the mentally retarded. In 1970, there were 10,136,000 women residing in the state of California. Therefore, there

is a 0.4 percent chance for any woman in the state to be in a state institution for the mentally retarded at some time during her life. Conversely, any normal California female would then possess a 99.96 percent chance of *not* residing in a state mental institution. For XXX females there would be a 99.86 percent chance of *not* residing in a California mental institution. These figures correspond to 16 XXX women in state mental institutions out of the theoretical possibility that approximately 10,000 XXX women reside in the state (XXX frequency: 1 per 1,000 females). Since there is only a 0.10 percent greater chance for an XXX female to be in an institution for the mentally retarded compared with XX females, this particular sex chromosome aberration does not appear to significantly increase the probability for admission to a hospital.

It is known that the average length of stay for both men and women patients in California state mental institutions is 322 days. This turnover rate shows that there are probably more mentally retarded XXX females in the general population than estimated above. Thus, using the probabilities for admission to an institution can only give an approximation of the chances that an XXX female will not have a developmental disability. One must also bear in mind that chi-square analysis strongly suggests a significance to the frequency of XXX females in mental institutions.

In examining the mental development of XXX females, Close and co-workers[7] have discovered two apparently normal XXX females, one during a routine examination. Kohn,[9] Kadotani[14] and Fujita[26] have also reported XXX females of normal intelligence. Robinson, Harris and Puck at the University of Colorado Medical Center (personal communication) have detected 12 XXX infants during consecutive newborn studies (40,000) from 1964 to 1974. One infant died in the neonatal period. Seven of these girls have been tested by the Wechsler Preschool and Primary Scale of Intelligence with quotients of 109, 109, 96, 96, 89, 82 and 76. Two had significant delays in language ability development and two had mild perceptual difficulties. These results are not significantly lower than their siblings' scores. It is anticipated that with the complete results of Robinson, Puck and co-workers, further insight about the mental capabilities of these children will be learned.

Maternal age appears to be important in discussing XXX female infants, but to a lesser extent than that found associated with the mothers of children with Down's syndrome. The cumulative combined results of 152 cases of XXX children show a median maternal age at the infant's birth to be 29 years. The median maternal age for 28 cases discovered during consecutive newborn studies is 25 years. Both of these results are higher than the California median maternal age which is in the range of 20 to 24 years, but the variance may be due to the small sample size. It would be informative to know the average maternal age for patients in institutions. If this number is significantly higher than the median maternal age of the population, then maternal age for XXX infants may possibly be related through other effects to mental disease. If the maternal age for patients in institutions is not higher than that for the general population, the increased maternal age in XXX cases may be thought to be related to a small sample size. We have not found any information regarding the maternal age for patients in institutions.

Conclusion

In conclusion, the XXX chromosome abnormality is found randomly with a frequency of approximately one per 1,000 in the general population and four per 1,000 in institutionalized patients. There does not appear to be any strong correlation between these two populations, because of the relatively small number of mental retardates in institutions. Information to date from consecutive newborn studies shows that intelligence quotients of the tested XXX children appear to be within the normal range. Increased maternal age is possibly associated with XXX children, but the effects of this remain unknown. Until more data become available, it seems reasonable to advise parents that probabilities favor normal intellectual development with an XXX karyotype although the risk for developmental disabilities may be higher for the XXX than for the XX fetus.

For all prenatal counseling in pregnancies at high risk for chromosome abnormalities, couples should be advised that an abnormal karyotype might not necessarily mean an unequivocally defective fetus. At the same time, assurance of a normal infant bearing an abnormal karyotype is probably impossible to guarantee. In these extremely sensitive considerations it is crucial that the primary genetic counselor be skilled in his interpretation of all available data, use every consultation source possible, be able to communicate

effectively and above all else, be sensitive to the feelings, needs and degree of understanding of the couple he counsels.

REFERENCES

1. Hamerton JL, Jacobs PA, Klinger HP (Eds.): Paris Conference (1971), Standardization in human cytogenetics, Birth Defects: Original Article Series, Vol 8, #7. White Plains, The National Foundation, 1973

2. Jacobs PA, Bailie AG, Court-Brown WM, et al: Evidence for the existence of the human "super-female". Lancet 2:423-425, 1959

3. Jacobs PA, Harnden DG, Court-Brown WM, et al: Abnormalities involving the X chromosome in women. Lancet 1:1213-1216, 1960

4. Day RW, Wright SW, Koons A, et al: XXX, 21-trisomy and retinoblastoma. Lancet 2:154-155, 1963

5. Ricci N: XXX 18-trisomy. Lancet 2:1276-1277, 1963

6. Anderson IF: The triplo-X syndrome: Clinical and cytological features. S Afr Med J 39:841-844, 1965

7. Close HG: Two apparently normal triplo-X females. Lancet 2:1358-1359, 1963

8. Stewart JSS, Sanderson AR: Fertility and oligophrenia in an apparent triplo-X female. Lancet 2:21-23, 1960

9. Kohn G, Winter JSD, Wellman WJ: Trisomy X in three children. J Pediat 72:248-252, 1968

10. Johnston AW, Ferguson-Smith MA, Handmaker SD, et al: The triplo-X syndrome. Brit Med J 2:1046-1052, 1961

11. Breg WR, Cornwell JG, Miller OJ: The association of the triple-X syndrome and mongolism in two families. Am J Dis Child 104:534-535, 1962

12. Day RW, Larson W, Wright SW: Clinical and cytogenetic studies on a group of females with XXX sex chromosome complements. J Pediat 64:24-33, 1964

13. Uchida A, Lewis AJ, Bowman JM, et al: A case of double trisomy: Trisomy No. 18 and triplo-X. J Pediat 60:498-502, 1962

14. Kadotani T, Ohama K, Makino S: A case of 21-trisomic Down's syndrome from the triplo-X mother. Proc Jap Acad 46: 709, 1970

15. Raphael T, Shaw MW: Chromosome studies in schizophrenia. JAMA 183:1022-1028, 1963

16. Barr ML: The sex chromosomes in evolution and medicine. Canad Med Ass J 95:1137-1148, 1966

17. Hienz HA, Michael CM, Schulz FW, et al: Zur trisomie des X chromosoms. Klin Wschr 41:996-1001, 1963

18. Barr ML, Sergovich FR, Carr DH, et al: Triplo-X female: An appraisal based on a study of 12 cases and a review of literature. Canad Med Ass J 101:247-258, 1969

19. Fraser JH, Campbell J, Macgillivray RC, et al: The XXX syndrome frequency among mental defectives and fertility. Lancet 2:626-627, 1960

20. Hamerton JL, Jagiello GM, Kirman BH: Sex chromosome abnormalities in a population of mentally defective children. Br Med J 5273:220-223, 1962

21. Maclean N, Mitchell JM, Harnden DG, et al: A survey of sex chromosome abnormalities among 4514 mental defectives. Lancet 1:293-296, 1962

22. De la Chapell A: Sex chromosome abnormalities among mentally defectives in Finland. J Ment Defic Res 7:129-146, 1963

23. Ridler MA, Shapiro A, McKibben WR: Sex chromatin abnormalities in female subnormal patients. Br J Psychiatry 109: 390-394, 1963

24. Anderson IF, Goeller EA, Wallace C: Sex chromosome abnormalities in a population of 1,662 mental defectives. S Afr Med J 38:346-349, 1964

25. Breg WR, Castilla EE, Miller OJ, et al: Sex chromatin and chromosome studies in 1,562 institutionalized mental defectives. J Pediat 63:738-739, 1963

26. Fujita H, Yoshida Y, Tanigawa Y, et al: A survey of sex chromosome anomalies among normal children and mental defectives. Jap J Hum Genet 16:198-211, 1972

27. Maclean N, Harnden DG, Court-Brown WM: Abnormalities of sex chromosome constitution in newborn babies. Lancet 2: 406-408, 1961

28. Mikamo K: Sex chromosomal anomalies in newborn infants. Obstet Gynecol 32:688-699, 1968

29. Robinson A, Puck TT: Studies on chromosomal nondisjunction in man II. Am J Hum Genet 19:112-129, 1967

30. Robinson A, Goad WB, Puck TT, et al: Studies on chromosomal nondisjunction in man III. Am J Hum Genet 21:466-485, 1969

31. Lubs HA, Ruddle FH: Chromosomal abnormalities in the human population: Estimation of rates based on the New Haven newborn study. Science 169:495-497, 1970

Medical
PROGRESS

Refer to: Barrett-Connor E: Advice to travelers (Medical Progress).
West J Med 123:22-30, Jul 1975

Advice to Travelers

ELIZABETH BARRETT-CONNOR, MD, *La Jolla, California*

Travelers, particularly those whose tastes or occupations lead to deviation from the usual tourist routes, are at a small but significant risk of acquiring certain diseases they would be unlikely to encounter had they remained in the continental United States. Many of these infections can be rendered unlikely even for the most adventuresome traveler through the appropriate use of immunization and chemoprophylaxis. Other infections are currently unpreventable and the physician's responsibility lies in their premorbid detection.

THIS REVIEW will consider advice to travelers visiting countries where the risk of acquiring certain infectious diseases exceeds the risk within the continental United States, as well as a program for evaluating the traveler after return to this country. Unavoidable generalizations have been made: Advice should be tailored to the individual traveler, taking into account the proposed itinerary and life style of the traveler; the latter may influence the risk of exotic disease to a degree at least as great as the countries visited. A physician must tread a thin line between creating neurotic travelers and preventing avoidable morbidity.

Required Immunizations

Immunization can be required by international law only for smallpox and yellow fever. In 1974 the World Health Organization determined that cholera vaccine can no longer be required by international law. This regulation has not yet been ratified by all countries and as of January 1975, a valid International Certificate of Vaccination showing cholera immunization is still required by 29 countries (Table 1).

Smallpox and cholera vaccine can be given by any licensed physician. The International Certificate of Vaccination (yellow card) must be completed and signed by the physician (signature stamps are unacceptable) and must be validated by an official stamp. Validation can be obtained at most local or state health departments. In California, physicians can request an official stamp from the state health department for use in their office. Yellow fever vaccinations currently must be given at an officially designated Yellow Fever Vaccination Center, usually a health department or clinic. Only immunization against smallpox, yellow fever and cholera need be recorded on the

From the Departments of Community Medicine and Medicine, University of California, San Diego, School of Medicine, La Jolla.
Reprint requests to: E. Barrett-Connor, MD, Department of Community Medicine, University of California, San Diego, School of Medicine, La Jolla, CA 92037.

HEALTH SCIENCES LIBRARY
UNIVERSITY OF MARYLAND
BALTIMORE

International Certificate of Vaccination. Details of immunization requirements and contraindications for these three vaccines are given in Table 2.

In general, travel directly from the United States to European countries, Canada, Mexico or the Carribean does not require an International Certificate of Vaccination. Travel between some of these countries may require a valid certificate of immunization. Vaccine requirements for travel to specific countries and between countries have been reviewed recently by a new *Health Information for International Travel,*[1] published annually by the Center for Disease Control. The *Morbidity and Mortality Weekly Report* from the same source updates interim changes in disease distribution and vaccine requirements. Current information usually can also be obtained from local health departments. These sources also provide information on the location and schedules of Yellow Fever Vaccination Centers.

Smallpox

In 1971 the United States Public Health Service determined that the risk of smallpox in the United States was less than the risk of untoward reaction to routine immunization; it was estimated that 15 cases of smallpox would have to be imported annually to equal the frequency of life-threatening complications of smallpox vaccination.[2] The United States no longer requires proof of smallpox vaccination by international travelers except for those returning from any of the three countries where smallpox transmission still occurs —India, Bangladesh and Ethiopia. Immunization against smallpox is required for entry into any of these countries, and is still required for entry into many countries without smallpox. For example, a smallpox vaccination is required for travel directly from the United States to most countries in South America, Africa and the Orient.

Vaccination is accomplished by a multiple pressure or multiple puncture technique *on dry skin.* A vaccine-impregnated pronged fork, available as a kit, gives a high yield of successful vaccinations. At primary immunization, failure to produce a vesicle is read as vaccine failure and requires revaccination. Examination of a revaccination is not required by law, but is strongly recommended; if no major reaction (vesicle, pustule, crust or ulcer) occurs, another vaccination should be given.

Contraindications to smallpox vaccination include pregnancy, atopy, eczema, and drug or disease associated immunosuppression. For example, patients with lymphoproliferative diseases should not be vaccinated and should not travel to countries with smallpox transmission. (Vaccinia-immune-globulin, [VIG, 0.3 ml per kg of body weight] can be given with primary vaccination to infants and to those with other contraindications who *must* travel to infected areas.[3]) Travel to countries without smallpox which require vaccination can sometimes be facilitated by a written statement from the physician on his letterhead delineating the medical contraindication to vaccination. Such documents, however, are not accepted by all countries, and it is best to check with the embassy concerned or with other informed sources on policies regarding unvaccinated aliens.

Yellow Fever

Yellow fever remains endemic in rural South America as far north as Panama and in tropical Africa. Travelers to these countries require immunization. Because of the long duration of protection and benign nature of the vaccine, vaccination is also recommended for travelers who may

TABLE 1.—*Cholera Vaccination Requirements—January 1, 1975**

I. Required of all travelers:
- Malawi
- Maldives
- Papua-New Guinea (except most countries in Oceania)

II. Required of travelers arriving from cholera infected areas:
- Albania
- Angola
- Brunei
- Cape Verde Island
- Egypt
- Fiji
- Iran [also from Afghanistan, Bahrain, Bangladesh, Burma, India, Iraq, Malawi, Malaysia, Pakistan, Philippines, Saudia Arabia, Singapore, Thailand, Vietnam (South)]
- Iraq
- Laos
- Libyan Arab Republic
- Macao
- Madagascar
- Namibia (by air)
- Nauru
- Oman
- Pitcairn Island
- Swaziland
- Zambia

III. Required of travelers arriving from countries any part of which is infected with cholera:
- Australia
- Christmas Island (also from Malaysia, Singapore)
- Guinea
- Italy (also from Guinea)
- Saudia Arabia

IV. Required only of travelers proceeding to a country with a cholera vaccination requirement:
- Burma
- India
- Nigeria

*From: Morbidity & Mortality Weekly Report 24:46, 1975.

change their itinerary en route to involve travel to countries with yellow fever.

Yellow fever vaccine is available only at designated sites and often only on certain specified dates. This is because the vaccine, as rehydrated for injection, loses its potency after one hour. The 17-D yellow fever vaccine offers nearly 100 percent protection for ten years and is one of the safest live vaccines in the world, the only contraindication being egg allergy. Persons allergic to egg should have this recorded on the yellow fever vaccination certificate by the health department. An adult traveler with egg allergy who must visit a yellow fever area can be immunized with a mouse brain vaccine available in French countries; children less than 14 years of age have a high incidence of encephalitis with this neurotropic vaccine and should not receive it.

Cholera

Cholera is again pandemic; in 1973 over 25 countries reported cases to the World Health Organization. Nevertheless, the risk of cholera in United States travelers with normal hygienic practices and normal gastric acidity is extremely small; less than ten North Americans have had recognized infection in the past ten years.[4] Cholera is poorly transmitted by contact and is primarily spread by ingestion of fecally contaminated water, fresh vegetables or seafood. The infectious dose of Vibrio cholerae is very large in comparison with other enteric pathogens.

Much of the cholera in the world today is caused by the El Tor strain. El Tor and classical cholera are antigenically similar and no special cholera vaccine is required for protection against El Tor. On the average, cholera vaccine offers about 50 percent protection in persons native to endemic areas who may have some acquired immunity.[5] Protection for nonimmune North Americans is presumably less. Protection is greatest the first month after vaccination and is negligible by six months. In addition to the low level of protection offered, vaccine side effects are common, over one quarter of the recipients developing a moderately severe febrile reaction.

Some countries with endemic or epidemic cholera and some unaffected countries still require proof of immunization. In some parts of the world failure to have a documented cholera immunization necessitates on-the-spot immunization (often with a needle of doubtful sterility), tetracycline or chloramphenicol prophylaxis and/or detainment

TABLE 2.—*Immunizations Which May Be Required*

Vaccine	*Type*	*Number of Required Injections*	*Route*	*When Certificate Is Valid*		*Protection (Approximate Percent)*	*Major Side Effects*	*Contraindications*
				*After Vaccination**	*Duration*			
Smallpox	Live	1	Multiple puncture or Multiple pressure	8 days	3 years	100	Encephalitis, vaccinia gangrenosa, disseminated vaccinia	<1 year of age, atopy, eczema, pregnancy, immunosupression
Yellow fever	Live	1	Subcutaneous	10 days	10 years	100	Fever myalgia, headache	Egg allergy ? Pregnancy
Cholera	Killed	1 or 2 (1-4 weeks apart)	Subcutaneous or Intramuscular	6 days	6 months	50	Fever, local pain	? Pregnancy

*Revaccination is valid immediately if last vaccination is within the interval noted above.

in quarantine camps for up to five days. Consequently, cholera vaccine is often recommended to protect the traveler from border immunization policy, if not from cholera itself.

Other Immunizations (Table 3)

Poliomyelitis

Persons who have already received a complete course of oral poliovirus vaccine should receive one additional dose of triple vaccine before travel to developing countries. This is not a booster dose, but serves to enhance the probability that antibody has developed to all three types of poliovirus. Persons who have not been immunized, who have received only parenteral poliomyelitis vaccine, or those whose immunization status is unclear, should receive a full course of oral poliovirus vaccine. There is a small risk of paralytic poliomyelitis following oral poliovirus vaccine; the risk is less than one case per million doses. Travelers must be informed of this risk and be advised that the risk is much less than the risk of paralytic poliomyelitis for a nonimmune person visiting an endemic area. Once a complete course of oral poliovirus vaccine has been completed no further poliovirus vaccine is required for subsequent travel.

Typhoid Fever

Typhoid fever is common in developing countries without adequate sanitary facilities. An increasing proportion of cases reported in the United States has been acquired during travel in other countries. Increasing numbers of chloramphenicol-resistant strains are being reported worldwide. Typhoid vaccine is therefore recommended for travelers to areas with poor food and water sanitation.

In clinical trials, protection following two doses of typhoid vaccine exceeds 70 percent and lasts for three to five years. The acetone-killed vaccine appears to be more protective than the heat-phenol vaccine, 93 percent versus 75 percent in one study.[6] Intradermal vaccination is said to produce fewer side effects than subcutaneous or intramuscular immunization; the acetone vaccine cannot be given intradermally. Presently available typhoid vaccine in the United States contains no paratyphoid antigen and causes fewer side effects than the old typhoid-paratyphoid vaccine.

Plague

Plague vaccine is not recommended for most visitors to countries with plague. It is recommended for travelers to the interior of Vietnam, Cambodia and Laos and to those whose occupation leads to frequent contact with wild rodents in plague enzootic areas of South America, Africa or Asia. Exact efficacy data are unavailable, but the rarity of plague in Americans in Vietnam, while several thousand cases were reported in the Vietnamese, suggests that the incidence and severity of plague are reduced following immunization.[7] Local pain and swelling are common; with repeated vaccination systemic signs of fever and headache also occur, but no permanent sequelae have been reported.

TABLE 3.—*Other Vaccines for Selected Travelers**

Vaccine	*Route*	*Number of Doses*	*Ideal Interval Between Doses*	*Booster*	*Efficacy (Approximate Percent)*	*Major Side Effects*
Trivalent Poliovirus.	by mouth	3 or 4	At least 3 weeks	None (see text)	95	Paralysis
Typhoid	subcutaneous or intradermal	2	At least 4 weeks	Every 3 years	75	Fever, pain
Plague	intramuscular	2 or 3	At least 3 weeks	Every 6 months	?	Fever, pain
Typhus	subcutaneous	2	At least 4 weeks	Every 12 months	?	Pain, fever (do not use in persons allergic to eggs)
Rabies	subcutaneous	3	At least 1 week between first 2 doses and 3 months between 2nd and 3rd	Every 2 years	?	Pain, fever (do not use in persons allergic to eggs)

*This list includes only immunizations which would not be given to United States adults who do not travel; usually only poliovirus and typhoid vaccines are recommended for travelers (see text). Other generally recommended immunizations such as tetanus are not included.

Rabies

Most travelers to areas with epizootic rabies do not require rabies immunization. Vaccination may be considered for those who will live in parts of the world where rabies is a constant threat or those who will have close contact with animals in such areas. Rabies vaccination reduces the amount of postexposure prophylaxis required should a traveler be bitten by a rabid animal. If an adequate antibody titer has developed four weeks after the last of three doses of duck embryo vaccine, only a single booster is required following a casual exposure, or a five-day course of vaccine is required following a bite.

Rickettsial Disease

Vaccination against epidemic (louse-borne) typhus is sometimes recommended for civilian travelers visiting mountainous or highland cold climates where louse infestation occurs. The risk of typhus for American travelers is minimal; no case is known to have occurred in recent years. Typhus immunization should be considered for travelers to endemic areas where typhus exists only if they will have close contact with natives, such as those who will teach school or work in hospitals.

Hepatitis

Studies in the military and in missionaries suggest that little excess risk of hepatitis appears until after at least three and probably six months sojourn on foreign soil; the cumulative risk increases with the duration of residence thereafter.[8,9] Passive prophylaxis with gamma globulin therefore is not recommended routinely for travelers unless they anticipate an extended stay in endemic areas. The recommended adult schedule (5.0 ml serum globulin intramuscularly) must be repeated every four to six months and protects only against hepatitis A (infectious hepatitis). Some physicians recommend 2.0 ml of gamma globulin for travelers planning short trips to highly endemic areas, outside the usual tourist routes through major cities only. Children usually tolerate hepatitis well and prophylactic gamma globulin generally is not recommended for children.

Diphtheria and Tetanus

In the press of other required or recommended immunizations it is often forgotten that many North American adults have no immunity to diphtheria or tetanus. When the immunization schedule permits, diphtheria/tetanus (D-T) immunization is appropriate, particularly for travelers with unsupervised travel plans in developing countries.

Combined Immunizations

Travelers often seek immunization shortly before their date of departure, requiring that more than one vaccine be given at the same time. There is no evidence that this is dangerous or that the resultant antibody response is altered. Smallpox, yellow fever, cholera and typhoid vaccine have been given concurrently at different sites. When possible, one avoids simultaneous use of vaccines which cause febrile reactions. Thus, typhoid and cholera vaccine ideally are given separately, and far enough ahead of the departure date so that side effects will not appear during travel.

Ideally, gamma globulin should not be given concurrently with other immunizations, although there is no documented evidence that gamma globulin inhibits antibody production following any live virus vaccine except measles. Because the protective value of gamma globulin is short-lived, it should be given last in any immunization series, as close to departure as possible.

Tuberculosis

Tuberculosis is an airborne disease transmitted to susceptible persons who have close association with sputum-positive cases. Tuberculin-positive persons are rarely susceptible to new infection, but tuberculin-negative travelers who will live with populations which have inadequate tuberculosis control programs may be infected; no precise data on this risk are available. Tuberculin-negative persons can be managed by skin testing eight weeks following return to the United States—for travelers with less than six months exposure—or every six months to one year while abroad. Conversions of the tuberculin test should be followed by appropriate chemoprophylaxis. Alternatively, tuberculin-negative travelers can be immunized with bacille Calmette Guérin (BCG) vaccine; the exact efficacy of the BCG vaccines currently available in the United States is unknown. BCG can be given safely at the time of other immunizations.

Chemoprophylaxis

Malaria

The rationale for malaria prophylaxis has been reviewed recently.[10] Countries with malaria trans-

TABLE 4.—*Countries with Malaria Transmission**

Africa
All countries except island territories and Spanish Sahara

North and Central America including Caribbean Islands
British Honduras, Costa Rica, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama

South America
All countries except Chile and Uruguay

Asia
All countries except Brunei, Cyprus, Israel, Japan, Kuwait, Lebanon, Macao, Mongolia, Ryukyu

Europe and USSR
Greece and USSR (limited distribution)

Oceania
British Solomon Islands, New Hebrides, Papua New Guinea

*From: Chemoprophylaxis of Malaria for Travelers.[10]

mission are indicated in Table 4. Most tropical and semitropical countries still have areas of malaria transmission. The risk is greatest for travelers who visit rural lowland (less than 1,600 feet) areas after dusk. Visitors confined to most urban centers are at little risk.

Appropriate chemoprophylaxis almost entirely prevents the development of potentially fatal falciparum malaria and suppresses clinical manifestations of other types of malaria as well. Chloroquine is the most reliable prophylactic agent, affording prophylactic suppressive cure of all sensitive strains of falciparum malaria and suppression with occasional cure of other human malarias (Table 5). Chloroquine is taken weekly, beginning one to two weeks before possible exposure (to ensure drug tolerance and to instill drug taking habits) and is continued for four to eight weeks after the last exposure. A 14-day course of primaquine (15 mg base daily) after the last possible exposure affords a prophylactic radical cure of vivax, malariae and ovale malarias. An alternate program is weekly administration of chloroquine and primaquine in a combined tablet continued for eight weeks after the last exposure; this regimen also provides radical cure of malarias with a secondary exoerythrocytic cycle.

Currently, there is no standard prophylactic regimen for travelers at risk to chloroquine-resistant falciparum malaria; in the military good results were obtained with weekly administration of chloroquine-primaquine plus daily dapsone. Dapsone prophylaxis carries a small but significant risk of agranulocytosis, which may be fatal. Therefore this regimen is indicated only for travelers to rural Southeast Asia and to limited highly endemic areas of Brazil, Colombia and the Philippines. It should be recalled that no chloroquine-resistant malaria has yet been documented in Africa or Central Asia, and that human malarias other than falciparum are not chloroquine resistant.

Amebiasis

Other than malaria, only two parasitic diseases, amebiasis and African trypanosomiasis, are preventable with currently available drugs. Amebiasis can be prevented with a luminal arsenical or a hydroxyquine; however, the former is associated with a risk of arsenic toxicity and the latter with subacute myelo-optic neuropathy, an occasionally irreversible neurologic disease.[11] In view of these hazards and the estimate that less than 2 percent of travelers acquire amebic infection, chemoprophylaxis cannot be recommended.

African Trypanosomiasis

Intramuscular pentamadine offers protection for six months against Trypanosoma gambiense, the cause of West African sleeping sickness, and may be considered for certain occupational groups at high risk to this infection.[11] If chemoprophylaxis is desirable, the injection must be obtained outside of the United States; in the United States pentamadine is available only as a therapeutic agent. Of the few North Americans who have acquired sleeping sickness, most have acquired East African trypanosomiasis (Trypanosoma rhodesiense)

TABLE 5.—*Malaria Chemoprophylaxis (Chloroquine-sensitive Strains)*

Drug (Brand Name)	*Adult Dose (base)*	*Pediatric Dose by Age in Years (base)*				*Interval*	*Duration After Last Exposure (days)*
		9-12	*5-8*	*1-4*	*Less Than 1*		
Chloroquine base (Aralen®)*.	300 mg	200-300 mg	150-200 mg	50-100 mg	37.5-50 mg	Weekly	28-56
or							
Chloroquine/primaquine base.	300/45 mg	300/45 mg	?	?	?	Weekly	56

*Does not offer radical cure of vivax, malariae or ovale malarias.

TABLE 6.—*Water Purification with Readily Available Chemicals**

Source	Drops to be added per quart (1 drop=0.05 ml) Clear Water	Cloudy Water
Liquid laundry bleach:		
Available chlorine (read label)		
1 percent or unknown	10	20
4-6 percent	2	4
7-10 percent	1	2
Tincture of iodine		
2 percent	5	10

*From: Health Information for International Travel.[1]

while on safari. No comparable clinical trials document the efficacy of pentamadine against this form of sleeping sickness, and there is at least a theoretical risk of cryptic infection with delayed diagnosis. Consequently, prophylaxis against sleeping sickness is not recommended for travelers to Africa except for the few whose occupation places them at risk to West African sleeping sickness.

Travelers' Diarrhea

The most common illness of travelers is travelers' diarrhea. This self-limited gastrointestinal illness, probably caused by acquisition of enteropathogenic Escherichia coli, is most common in young adults. Several clinical trials have shown that some nonabsorbable antimicrobials, most notably neomycin or a sulfa drug, afford 60 percent protection and may also reduce the severity of diarrhea in those affected.[12] The unsupervised use of antimicrobials, however, is probably more hazardous than the self-limited illness these drugs are intended to prevent. There is a theoretical risk that antimicrobial-suppression of normal enteric flora will enhance susceptibility to other intestinal pathogens. Therefore, chemoprophylaxis for travelers' diarrhea is not recommended for general use. Chemoprophylaxis may be indicated for limited use, such as in a brief business trip where a bout of diarrhea would preclude the entire purpose of the travel. It should be recalled that iodochlorhydroxyquin (Entero-Vioform®), frequently used for chemoprophylaxis, offers no protection and may be dangerous.

General Precautions

Travelers should be advised to avoid fatigue and excessive use of alcohol. A few may actually heed such instruction. In addition, it is appropriate to advise travelers to avoid water of uncertain quality; in most countries outside of North America, tap water should be suspect. Available evidence suggests that the avoidance of tap water in certain parts of the world, for example, Leningrad, would prevent diarrhea caused by Giardia lamblia.[13] Many travelers do not know that ice is often made from contaminated water or that bottled water may be bottled directly from the tap. Travelers should also avoid eating of uncooked fruits or vegetables unless they can be peeled at the table. Precautions against tap water, salads, and so forth, have not been shown to reduce the incidence of travelers' diarrhea,[14] but they probably reduce the risk of more serious enteric infections which require a larger infectious dose. Boiled beverages (such as coffee or tea), carbonated beverages and wine or beer are usually safe. The addition of chlorine (Halazone®) or preferably iodine (Globaline®) tablets to tap water is recommended when no reliable source of water is available. When such tablets are unavailable, liquid chlorine (as in laundry bleach) or tincture of iodine can be added to the water (Table 6).

Travelers to countries with insect-borne diseases should be advised about the value of protective clothing, insect repellants liberally and repeatedly applied, staying indoors in the evening, and the use of screens and netting when in rural areas. *Finally, advice to travelers should include the precautionary note that no preventive measure is guaranteed, and that any subsequent illness should prompt the traveler to include a travel history in his chief complaint.* All travelers whose itinerary or lifestyle suggests a greater than usual risk should be advised to have a checkup on return to the United States.

Obtaining a Physician in a Foreign Country

Travelers should know the basis of obtaining competent medical care unless their travel plans offer such services, as provided by most large hotels and cruise ships. Information can be obtained before travel from international registers of medical speciality board members. During travel the names of qualified physicians can be obtained from the overseas offices of traveling businessmen and from the United States Consulate or the nearest university hospital.

Travelers should be warned that potentially dangerous drugs such as chloramphenicol, butazolidin and aminopyrine may be found in cold and fever remedies or prescribed for nonspecific illnesses in some countries. Foreign physicians may

prescribe drugs not yet admitted to the American market; in many countries there are no proof of efficacy or safety requirements for drugs sold by prescription or over the counter. Except under extreme circumstances, travelers should refuse parenteral medications from physicians or pharmacists in any setting where the sterilization of needles is questionable. (Previously it was possible to give the traveler a disposable syringe and needle to meet such emergencies; however, with increasing concern over narcotics this approach may now cause difficulties at the border not always remedied by a letter of intent by a physician.) In many countries it is possible to purchase a new needle and syringe over the counter.

Medical Kits

Physicians are sometimes asked to suggest the content of medical kits to permit self-treatment of maladies acquired during travel. This is usually risky, inappropriate treatment often exacerbating or masking problems, and it is preferable that ill travelers seek the assistance of a physician. A medical kit is appropriate, however, for travelers visiting remote areas where no source of medical care is available. In addition to bandages and antiseptics, such kits should contain a nonnarcotic pain medication (a simple toothache up the Amazon can be devastating), an antibiotic-antifungal ointment and a broad spectrum oral antibiotic (such as tetracycline or ampicillin) with clearly written guidelines for its use. No antibiotic has proven efficacy for travelers' diarrhea, and travelers should be advised not to take antimicrobials for diarrhea of less than three days duration unless dysentery is present. Although frequently recommended, the value of antidiarrheal agents such as paregoric and diphenoxylate hydrochloride with atropine sulfate (Lomotil®) can be questioned because such agents may increase the duration or severity of some infectious diarrheas.[15] Additional contents of the medical kit, such as anti-snake venom, are rarely practicable unless the group will be accompanied by someone with medical training. All medications should be clearly labeled.

The Traveler Returned

Apparently healthy travelers returning from developing countries should be screened for diseases which they may have acquired en route. The usual evaluation includes a complete blood count, using anemia as a marker for chronic disease and eosinophilia as a marker for most nonprotozoal parasites. Stool specimens should be examined for ova and parasites in order to identify parasites which merit treatment in the absence of illness; these are Entamoeba histolytica, Strongyloides stercoralis, Ascaris lumbricoides and tapeworms. (Asymptomatic infections with hookworm, Trichiuris and Giardia do not require therapy.) Tuberculin-negative travelers closely exposed to the residents of developing countries should also have a tuberculin test eight weeks after the last exposure.

Travelers who become ill after return to the United States usually present with fever or diarrhea or both. Travelers with fever who have visited areas of malaria transmission should be suspected of having malaria, whether or not antimalarials were taken. Blood smears should be obtained immediately. It is dangerous and unnecessary to wait for the next fever spike; indeed, malaria parasites are most difficult to identify at the peak of fever. Malaria in nonimmune persons may never show a classical fever pattern, splenomegaly is not an early finding in many cases, and falciparum malaria can be fatal within 48 hours of illness.

An amebic liver abscess is the other very important cause of fever in a returned traveler. Tests of stool specimens give negative findings for E histolytica in at least half of the cases. Although hepatomegaly or abnormal findings on liver function tests may suggest the correct diagnosis, they may be absent. A liver scan and amebic serology are required to exclude this life-threatening possibility.

Patients with diarrhea which has persisted for more than three days, or contains blood, or is associated with high fever, should be evaluated for enteric pathogens. The most common of these are Salmonella, Shigella, E histolytica and Giardia. Fortunately, cholera importation into the United States is extremely rare. However, an abrupt onset of profuse watery diarrhea within five days of leaving a country with cholera requires a stool culture on appropriate media. It is important to recall that the usual selective media for enteric pathogens are not satisfactory for the recovery of Vibrio cholerae or Shigella dysenteriae. Patients with diarrhea should not receive antibiotics until stool specimens have been examined for protozoa; many antimicrobials render the diagnosis of intestinal amebiasis impossible without affording a cure.

A variety of other less common exotic causes

of diseases of travelers can be considered when malaria and extraintestinal amebiasis have been excluded. These have been reviewed elsewhere.[16,17]

REFERENCES

1. United States Dept of Health Education & Welfare, Public Health Service: Health information for international travel. Morbidity & Mortality Weekly Report 23:1-76 (Supplement) Sep 1974

2. United States Dept of Health Education & Welfare, Public Health Service: Public health service recommendation on smallpox vaccination. Morbidity & Mortality Weekly Report 20:339-345, 1971

3. Lane JM: Protection of eczematous child requiring smallpox vaccination before foreign travel. JAMA 227:448, 1974

4. Gangarosa EJ, Faich GA: Cholera: The risk to American travelers. Ann Intern Med 74:412-415, 1971

5. Joo I: Cholera vaccines, *In* Barua D and Burrows W (Eds): Cholera. Philadelphia, W B Saunders Co., 1974, pp 333-355

6. Ashcroft MT, Singh B, Nicholson CC, et al: A seven-year field trial of two typhoid vaccines in Guyana. Lancet 2:1056-1059, 1967

7. Cavanaugh DC, Elisberg BL, Llewellyn CH, et al: Plague immunization—V. Indirect evidence for the efficacy of plague vaccine. J Infect Dis 129:(Suppl)S37-S40, 1974

8. Cline AL, Mosley JW, Scovel FG: Viral hepatitis among American missionaries abroad. JAMA 199:551-553, 1967

9. Woodson RD, Clinton JJ: Hepatitis prophylaxis abroad. JAMA 209:1053-1058, 1969

10. Barrett-Connor E: Chemoprophylaxis of malaria for travelers. Ann Intern Med 81:219-224, 1974

11. Barrett-Connor E: Chemoprophylaxis of amebiasis and African trypanosomiasis. Ann Intern Med 77:797-805, 1972

12. Barrett-Connor E: Travelers' diarrhea. Calif Med 118:1-4, Mar 1973

13. Walzer PD, Wolfe MS, Schultz MG: Giardiasis in travelers. J Infect Dis 124:235-237, 1971

14. Loewenstein MS, Balows A, Gangarosa EJ: Turista at an international congress in Mexico. Lancet 1:529-531, 1973

15. DuPont HL, Hornick RB: Adverse effects of Lomotil therapy in shigellosis. JAMA 226:1525-1528, 1973

16. Barrett-Connor E: Exotic infections as seen in travelers. J Florida Med Assn 56:709-714, 1969

17. Gilbert DN, Moore WL Jr, Hedberg CL, et al: Potential medical problems in personnel returning from Vietnam. Ann Intern Med 68:662-678, 1968

Refer to: Pulmonary vascular disease—Medical Staff Conference, University of California, San Francisco. West J Med 123: 31-40, Jul 1975

Pulmonary Vascular Disease

These discussions are selected from the weekly staff conferences In the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The diagnosis of a massive pulmonary embolus usually offers little difficulty for the internist. It is much more difficult, however, to suspect and to document the recurrence of multiple small pulmonary emboli. The latter continuing disorder may be even more serious for the patient. We have asked Dr. Homer Boushey to review this topic for us with particular emphasis on what can be learned from modern techniques of pulmonary function testing.*

DR. BOUSHEY:† Pulmonary vascular disease results from any condition which causes occlusion or narrowing of the pulmonary blood vessels. Because the lungs are the only organ through which the entire cardiac output passes, and because the lungs are a major interface between ourselves and our environment, it is not surprising that the number of conditions which can cause pulmonary vascular disease is extraordinarily large. These include congenital heart disease with left to right shunts, collagen vascular diseases, the pneumoconioses, emphysema, multiple recurrent pulmonary emboli, intravenous drug abuse, drug reactions and many others.

The abnormalities in the pulmonary vessels themselves cause only nonspecific symptoms and signs which tend to occur late in the history of the disease. The possibility that the pulmonary vessels may be damaged is usually inferred from findings in other organs; for example, the finding of an opening snap in mitral stenosis, or the discovery of the skin, joint and renal changes of systemic lupus erythematosus. When the pulmonary vessels are themselves the primary site of damage the disease is particularly difficult to diagnose, as is the case in primary pulmonary hypertension or pulmonary vascular disease due to multiple recurrent pulmonary emboli. Today, I wish to focus on these two elusive diagnostic problems.

Because Dr. Warren Gold discussed primary pulmonary hypertension here fourteen months ago, I am going to focus primarily on multiple recurrent pulmonary emboli as a cause of pulmo-

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Homer Boushey, MD, Assistant Professor of Medicine, Co-director of the Pulmonary Function Laboratory.

ABBREVIATIONS USED IN TEXT

A-V = atrioventricular
FEV_1 = forced expiratory volume in one second
FVC = forced vital capacity
pCO_2 = carbon dioxide partial pressure
pH = hydrogen ion concentration
pO_2 = oxygen partial pressure
VD/VT = ratio of wasted ventilatory volume to tidal volume

nary vascular disease. In doing this, I wish to reverse the usual sequence of Grand Rounds. I plan first to present the physiological and clinical features of the disease, and then shall end my discussion by presenting two cases which we have recently seen on the Chest Service.

The pulmonary vascular bed must accept the entire cardiac output, and because the cardiac output can increase up to fivefold with exercise, the pulmonary vessels have evolved in such a way that they can accept large changes in flow with only small changes in pressure.[1] When the change in mean pulmonary artery pressure is plotted against change in pulmonary blood flow (Figure 1), it is apparent that pulmonary arterial pressure increases little with a doubling in perfusion of the pulmonary vascular bed. It is only when flow is more than two and a half times control that further increase in flow causes a brisk rise in resistance.

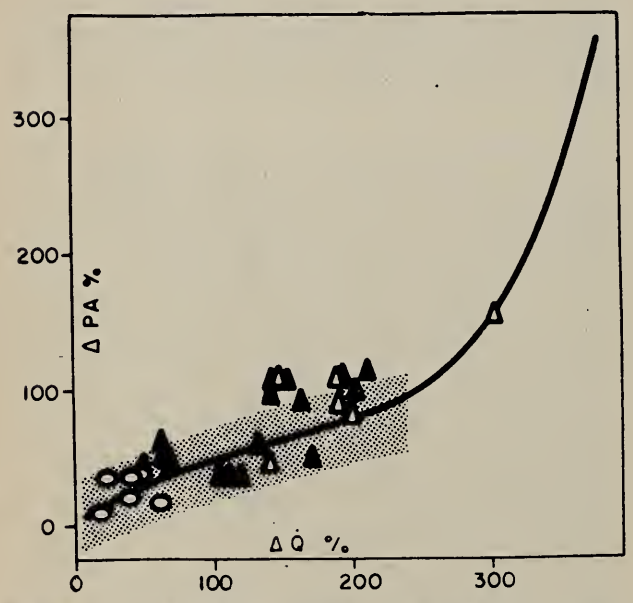


Figure 1.—Relationship between pulmonary blood flow and pulmonary arterial pressure. Note that the origin represents normal or control levels (not zero levels) of both pressure and flow. (From Fishman AP: Dynamics of the pulmonary circulation, chap 48, **In** Handbook of Physiology—Vol 2, Section 2: Circulation. Washington, DC, American Physiol Soc, 1963, pp 1667-1743)

This behavior explains why a patient is able to survive a pneumonectomy without suffering from intolerable pulmonary hypertension. The remaining lung is able to accept a doubling of flow with only a small increase in pulmonary arterial pressure. The converse is also true. If persistent pulmonary hypertension has resulted from a pulmonary embolus, then more than 60 percent of the vascular bed has been obstructed.

The lung is so successful in accommodating large changes in flow that pulmonary vascular resistance actually falls as cardiac output increases. Resistance is defined as the change in pressure per unit flow, and for the lungs is represented by the difference between the mean pulmonary arterial pressure and mean left atrial pressure divided by the cardiac output. At rest, typical values might be pulmonary arterial pressure of 15 mm, a left atrial pressure of 6 mm and a cardiac output of 6 liters per minute. The resistance calculated from these values is low, only 1.5 units. With modest exercise, causing doubling in the cardiac output, pulmonary arterial pressure rises slightly so that the driving pressure per unit flow actually falls. The lung achieves this fall in resistance by recruiting additional pulmonary capillaries in its vascular bed, particularly in the upper portions of the lung. At rest, the upper portions of the lung are not well perfused but as cardiac output rises, the very small increase in pressure is enough to perfuse this region, and the total cross-sectional area of the capillary bed available for perfusion increases. These observations suggest that pulmonary hypertension usually results from an abnormal increase in pulmonary vascular resistance. It is only rarely that an increase in flow is itself enough to cause pulmonary hypertension. In studying the mechanism of production of pulmonary hypertension one therefore looks at the causes of an increase in pulmonary vascular resistance.

Pulmonary vascular resistance is increased when the cross-sectional area of the pulmonary vascular bed is reduced, as in emphysema (in which lung parenchyma is actually destroyed), in fibrotic lung diseases and in multiple recurrent pulmonary emboli (in which the pulmonary vascular bed is obliterated from within). Arterial and arteriolar thickening may be the primary event. This clearly occurs in primary pulmonary hypertension, a rare disease of unknown cause in which the initial event is thickening of the resistance vessels; that is, pulmonary arteries and arterioles.

When the pulmonary vessels are exposed to a prolonged increase in pressure from any cause, similar reactive changes occur in these vessels, causing the development of irreversible pulmonary hypertension.

A third cause of increased pulmonary vascular resistance is an increase in arterial and arteriolar smooth muscle tone. This is of particular interest because it is potentially reversible. Hypoxia and acidosis have synergistic effect on pulmonary vascular smooth muscle, so that in a patient with chronic bronchitis admitted with hypoxia and respiratory acidosis, pulmonary hypertension is at least partially due to constriction of pulmonary vascular smooth muscle. Increasing arterial oxygen tension by giving supplemental oxygen and reducing elevated arterial carbon dioxide partial pressure (pCO_2) by aggressively treating the obstructive disease will reverse both causes of smooth muscle constriction, and pulmonary vascular resistance will fall. Associated right heart failure may then be reversed. I should also mention that the increase in the smooth muscle tone in both the pulmonary arteries and arterioles caused by hypoxia may account for some of the reversible pulmonary hypertension seen after an acute pulmonary embolus. Another possibility is that chemicals, such as serotonin, may be released from platelets adhering to a thrombus which lodges in the pulmonary circulation and may also cause constriction of arterial smooth muscle.

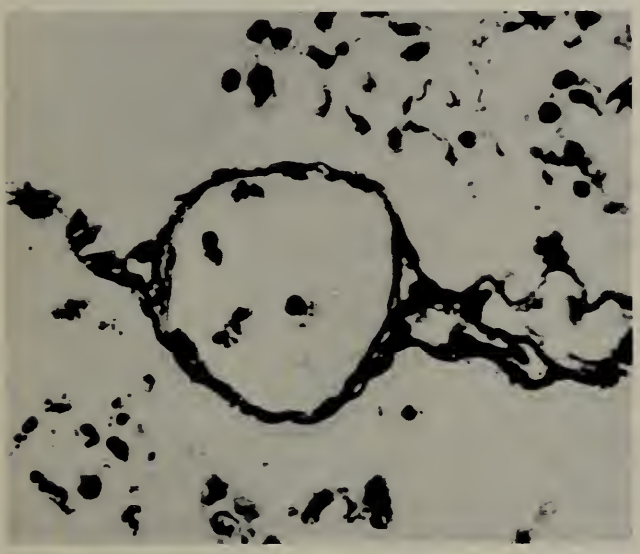


Figure 2.—Transverse section of a normal arteriole. There is a single elastic lamina between the endothelium and a very thin adventitia (From Harris P, Heath D: The Human Pulmonary Circulation. Edinburgh, Livingstone, 1962)

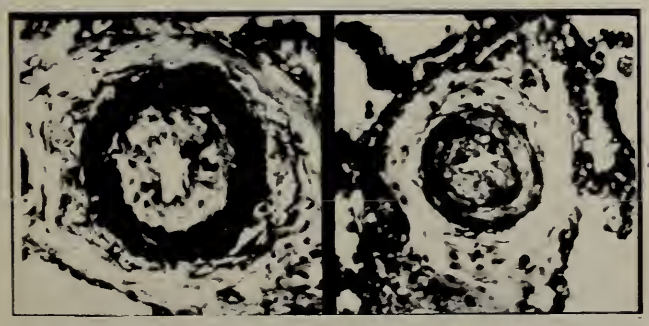


Figure 3.—**Left,** Transverse section of small pulmonary artery; **Right,** pulmonary arteriole from a patient with pulmonary hypertension. Thickening of the tunica media and intimal cellular proliferation are noteworthy (From Harris P, Heath D: The Human Pulmonary Circulation. Edinburgh, Livingston, 1962)

If pulmonary hypertension persists, characteristic pathological changes develop in the arteries and arterioles.[2] Figure 2 shows a typical pulmonary arteriole. It has a very thin wall and a sparse muscular coat. After prolonged exposure to increased pressure or flow there occurs great thickening of the tunica media and perhaps also fibroproliferation of the intima (Figure 3). Because much of the resistance to flow is located at the pulmonary arteries and arterioles, when these changes occur irreversible pulmonary hypertension has developed. Bearing this in mind, I would like to take a look at a classical or traditional system for classifying the pulmonary vascular diseases.

In this system pulmonary hypertension is classified as being postcapillary or precapillary depending upon the site of the initial pathologic disturbance. Precapillary forms include the congenital heart diseases which expose the pulmonary arteries and arterioles to increased flow or pressure, recurrent pulmonary emboli (in which the vascular bed is obliterated from within), primary pulmonary hypertension, and schistosomiasis (in which fibrosis around the arterioles causes initial narrowing of the cross-sectional area of the pulmonary vascular bed).

Postcapillary forms are those associated with an increase in left atrial or pulmonary venous pressure. The initial rise in pulmonary arterial pressure is greater than that which is strictly needed to maintain perfusion in the face of increased left atrial or pulmonary venous pressure. This rise is presumed to be caused by a reflex constriction of pulmonary arteries and arterioles. When this pulmonary hypertension persists long enough, there may be irreversible changes in the vessels, as are depicted in Figure 3, and irreversible pulmonary hypertension has developed.[2]

Whether the pulmonary hypertension is at a reversible or irreversible stage is a problem cardiologists must often face. But the point is that *postcapillary* forms of pulmonary hypertension are associated with changes in the *precapillary* vessels, whether they are reflex or are due to actual change in the structure of the vessels. Mixed forms are those in which the initial event really cannot be located precisely as precapillary or postcapillary.

Whatever the immediate or remote cause of the increase in pulmonary vascular resistance, the symptoms of pulmonary vascular disease are similar. Dyspnea is the cardinal feature of the disease.[3,4] It occurs early and may be episodic at the beginning, but becomes chronic as the disease progresses. It is particularly prominent on exercise. In young patients the dyspnea of pulmonary vascular disease is often confused with that of anxiety states, and people who are suffering from primary pulmonary hypertension or multiple recurrent pulmonary emboli are often labelled as psychoneurotic before the disease becomes apparent. The features of dyspnea may help distinguish between the two.

The dyspnea of pulmonary vascular disease is distinguished by its chronicity, its regularity and its worsening with exercise. The hyperventilation of anxiety states is usually episodic and irregular, and improves with exercise. Chest pain is not a particularly common symptom. When it does occur, it consists of a band-like tightness across the chest which is not promptly relieved by rest or nitroglycerin. Syncope is classically described in primary pulmonary hypertension, but may occur with pulmonary vascular disease from any cause; the mechanism of its production is unknown but may be related to the low cardiac output of these conditions.

Figure 4.—Posteroanterior chest radiograph of a patient with pulmonary hypertension, systemic lupus erythematosus and a patent ostium secundum defect. Note prominent central pulmonary arterial trunks with rapid tapering of vessels in the periphery.

Signs are similarly not specific. Cyanosis is rare but may occur when there is a patent foramen ovale which is present in up to 20 percent of normal people.[5] When right atrial pressure rises as the result of the increased load on the right heart caused by the increase in pulmonary arterial pressure, the normal gradient between the left atrium and right atrium is reversed and right to left shunting may develop. This may not occur until the patient exercises. In the absence of such a defect, cyanosis is distinctly unusual in pulmonary vascular disease and occurs only in the very late, preterminal stages of the disease. Specific chest findings are similarly absent.

Cardiac findings are predictable. They include an increased pulmonary component of the second sound, a right ventricular lift, a prominent "a" wave in the jugular venous pulse and signs of right heart failure if the load on the right heart has progressed to that point. Clubbing is often mentioned but rarely seen. When it does occur, the mechanism of its production is unknown.

Routine laboratory studies are not disturbed in the early stages of the disease, and this accounts for the difficulty in making the diagnosis. Findings on an electrocardiogram may show right axis deviation or right ventricular hypertrophy, but this does not occur until the disease has progressed considerably. A chest x-ray film may show enlarged pulmonary artery and rapid tapering of the pulmonary vessels in the periphery. The patient depicted in Figure 4 has systemic lupus and an atrioseptal defect (probably an ostium secundum defect) but one can certainly appreciate the immense size of the pulmonary arteries on both sides, yet the vascular markings are not especially prominent in the periphery. This rapid tapering from great dilatation to inconspicuous size is what radiologists refer to as pruning.

Routine pulmonary function studies of lung volume, flow and distribution of gas are normal.

The diffusing capacity may be reduced but is not reduced in all cases. I wish to emphasize that even if pulmonary vascular disease is due to multiple recurrent pulmonary emboli, the single breath diffusing capacity, a measure of the volume of blood in the alveolar capillaries, may be normal. A normal diffusing capacity does not exclude multiple recurrent pulmonary emboli. Additional studies can detect disordered ventilatory dysfunction, but these are not done as part of routine pulmonary function testing.

To describe these, I would like to imagine the lung as consisting of two giant alveoli, each of which receives half the ventilation and half of the perfusion. A normal tidal volume may be 450 ml. Of this 450 ml of inspired gas, 150 remains in the conducting airways, does not participate in gas exchange and is referred to as the dead space. To each half of this highly schematized lung, 150 ml is distributed. In this example the ratio of dead space to tidal volume is 33 percent (150/450 ml). Now if, as the result of the disease process, the perfusion of half the lung is obstructed, the gas which has gone to this portion of the lung also does not participate in gas exchange and acts as if it were in conducting airways. The dead space is now 150 ml in the airways plus 150 ml in the nonperfused alveoli, so the ratio of dead space to tidal volume is 67 percent (300/450).

One of the hallmarks, therefore, of pulmonary vascular disease is an increase in the ratio of dead space to tidal volume. If the subject wishes to maintain the same effective alveolar ventilation, he must double his total minute ventilation. So the second feature of pulmonary vascular disease is an increase in the minute ventilation for any level of activity.

For reasons that we do not completely understand, the patients with this disease not only increase their minute ventilation to the point where they maintain normal effective alveolar ventilation, but they go on beyond that, so that the blood gases typically show a compensated respiratory alkalosis due to chronic hyperventilation. This schema is neat, but of course it does not always happen this way. By constricting small airways the lungs are capable of shifting ventilation away from nonperfused areas, so that ventilation is re-

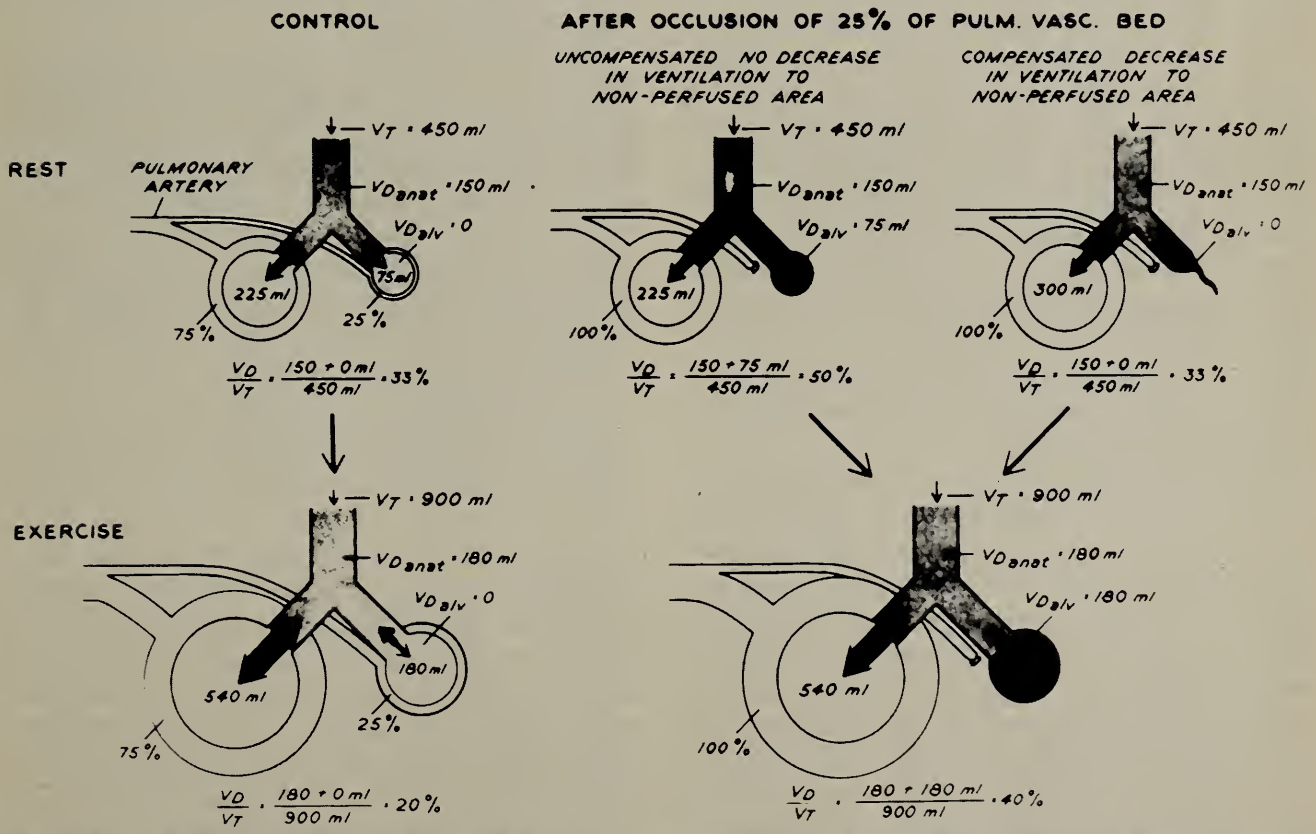


Figure 5.—Theoretical model comparing wasted ventricular volume and tidal volume (VD/VT) at rest and during exercise, before and after occlusion of 25 percent of the pulmonary vascular bed. Circular parts represent alveoli; one is 25 percent of the lung, the other 75 percent. These are connected to conducting airways (stippled areas). Arrows indicate magnitude of tidal volume during inspiration. Width of blood channels surrounding alveoli indicate volume of pulmonary capillary blood flow to each region. See text for explanation. (From Nadel JA, Gold WM, Burgess JH: Early diagnosis of chronic pulmonary vascular obstruction. Am J Med 44:16-25, Jan 1968)

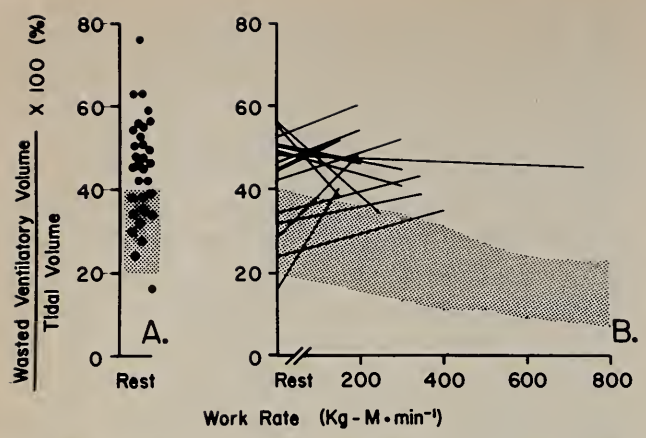


Figure 6.—Ratio of wasted ventilatory volume to tidal volume (VD/VT) in patients with pulmonary vascular disease at rest (A) and with exercise (B).

distributed to the perfused lung. If this occurs, and one measures the ratio of dead space to tidal volume, it may appear to be normal. When this happens, the abnormality can be brought out by stressing the system of exercising the patient.

In Figure 5 the lung is shown as a two-compartment model in which a quarter of the ventilation and perfusion go to one portion of the lung and three quarters to the other portion. The dark area shows the gas in dead space which is not communicating with the alveolar blood and which does not participate in gas exchange. The ratio of dead space (150 ml in connecting airways) to tidal volume, is 33 percent. When this person exercises, tidal volume increases from 450 to 900 ml. With this increase in tidal volume there is only a small increase in the size of connecting airways, say an additional 30 ml, so that the ratio of dead space to tidal volume falls. Under normal conditions exercise produces a fall in the ratio of dead space to tidal volume, in this example from 33 percent to 23 percent.

The middle panel shows that the nonperfused alveoli are normally ventilated, so that the gas that goes to these alveoli acts as dead space gas and the ratio of dead space to tidal volume is increased. The lung can, however, compensate as depicted by constricting the airways leading to nonperfused alveoli. Inspired air is thus shifted away from the nonperfused alveoli and goes only to those that are perfused. In this case, the ratio of dead space to tidal volume is absolutely normal. The difference is brought out by exercising the patient and putting the system under stress.

With the increase in tidal volume brought about by exercise the constriction of these airways is overcome and the nonperfused alveoli are then ventilated. Therefore, there is a great rise in dead space relative to tidal volume. Instead of falling with exercise, the ratio of dead space to tidal volume increases. In this example of the normal state it fell from 33 to 20 percent, and in the abnormal state increased from 33 to 40 percent.[3,6]

Another abnormality that may not be apparent until the patient has been exercised is a disorder in oxygen transfer. Normally, there are about 300 million alveoli in the lungs through which 60 ml of blood are distributed. When this is the circumstance, even with large increases in cardiac output, each red cell can spend enough time in capillaries to become fully saturated with oxygen. When the pulmonary capillary bed has been reduced, as by pulmonary vascular disease, the whole of the cardiac output must pass through fewer capillaries. When the cardiac output is increased, as by exercise, the only way it can be accommodated is by reducing the amount of time each red cell spends in capillaries and the red cells may leave the capillaries incompletely saturated. So one of the features of the disease in the exercise state is a fall in arterial oxygen tension due to a kind of diffusion defect.

The value of exercise testing is exemplified by the work of Gold, Nadel and Burgess reproduced in Figure 6.[3] Here can be seen the ratio of dead space to tidal volume in a number of patients with well documented pulmonary vascular disease. At rest (the shaded area is normal) the ratio of dead space to tidal volume is normal in many of the patients, but in every case when the subject was exercised the ratio of dead space to tidal volume increased above the normal range.

I will summarize the usual or characteristic findings on laboratory studies. An electrocardiogram may show signs of right ventricular hypertrophy or right axis deviation. On x-ray films of the chest, an enlarged pulmonary outflow tract, pruning of the vessels in the periphery and right ventricular hypertrophy are seen. Results of studies of arterial blood gases characteristically show chronic compensated respiratory alkalosis. Right heart catheterization may show pulmonary hypertension at rest. If it is not present at rest, it may be brought out with a modest amount of exercise. Pulmonary function studies at rest include normal volumes and flows, and occasionally a reduced diffusing capacity, but by no means in all cases. On exercise the hallmarks are hyperventilation at each level of activity, an increase

TABLE 1.—*Exercise Evaluation of 47-year-old Man with Multiple Pulmonary Emboli*

Work Load	*Rest*	*100 Kg-M/Min*	*300 Kg-M/Min*
pO_2	75	67	65
pCO_2	33	27	26
pH	7.41	7.41	7.37
$\dot{V}$ min (L)	11.3	27.8	60.8
VD/VT	.44	.42	.47

pO_2=oxygen partial pressure
pCO_2=carbon dioxide partial pressure
pH=hydrogen ion concentration
$\dot{V}$=ventilation
VD/VT=ratio of wasted ventilatory volume to tidal volume

in wasted ventilation shown by a rising wasted ventilatory volume to tidal volume (VD/VT) ratio and worsening hypoxemia with exercise.

I would now like to take a few minutes to present two cases which we have recently seen on our service with pulmonary vascular disease due to multiple recurrent pulmonary emboli.

The first case is that of a 47-year-old man who worked as a construction worker on a road gang. The patient was in a good state of health until January, 1968 when the 95 pound jackhammer he was operating jumped loose and struck him in the right thigh. There subsequently was pain, swelling and redness of the thigh. The patient called his physician and was advised to go to bed and wrap the leg with a hot towel. He did so and was able to return to work two days later, noting only a slight amount of stiffness in the leg.

Two weeks later he noted the onset of progressively worsening shortness of breath on exertion. By March he was unable to work and had lost 40 pounds. In April he consulted his physician, and results of pulmonary function studies done at his community hospital showed slight airway obstruction; the oxygen partial pressure (pO_2) was recorded as 49, but this may have been a venous sample.

In May a lung biopsy was done because it was thought that the patient had subradiographic interstitial pulmonary fibrosis. Findings on the lung biopsy showed arteriolar hypertrophy with only slight fibrosis and atelectasis. In July, for the first time, an increase in heart size was seen on an x-ray film of the chest. I would like to emphasize that this is now late in the course of the patient's illness. The electrocardiographic findings had changed and showed an incomplete right bundle branch block. It was then considered possible that the patient had pulmonary hypertension and findings on a right heart catheterization confirmed the diagnosis; cardiac output was low and pulmonary vascular resistance was grossly increased.

An angiogram was done which showed multiple vessel cutoffs demonstrating recurrent pulmonary emboli. The patient was treated with anticoagulation and inferior vena caval plication, and then referred here for further assessment of the degree of the pulmonary disability.

On the patient's arrival we first carried out screening pulmonary function studies. They are of interest because the results showed no abnormality. Total lung capacity, residual volume and vital capacity were all within normal ranges, diffusing capacity was normal, the forced expiratory volume in one second (FEV_1) in absolute values and as a percent of forced vital capacity (FVC) was normal. The single breath oxygen test was only very minimally disturbed. These would be read as minimal abnormalities, certainly insufficient to explain the shortness of breath. The patient was then exercised and the data were typical of the findings of this condition (Table 1). Arterial oxygen levels were slightly low at rest; the low pCO_2 with a normal hydrogen ion concentration (pH) showed chronic hyperventilation with renal compensation. With exercise the arterial oxygen levels fell slightly. Minute ventilation rose disproportionately to the level of exercise. At 300 kg meter per minute we would expect the normal person to ventilate about 25 liters per minute, and ventilation in our patient was well over twice the predicted level. The ratio of VD/VT, of dead space to tidal volume, was just above normal at rest, but rose abnormally with exercise.

The next patient is a 43-year-old woman who was admitted to the Surgical Service here for worsening shortness of breath and chest pain. Two months before this admission, the patient had been admitted for vaginal bleeding. At dilatation and curettage a large pulsatile mass was found in the right pelvis. An angiogram was scheduled and was done two weeks later. Findings on the angiogram showed a large arteriovenous (A-V) malformation apparently contained within the uterus. It was decided to remove this surgically, but before operation the arterial supply to this A-V malformation was catheterized and an embolization was carried out with the injection of lead beads, gelfoam and cotton fibers, in an attempt to obstruct the A-V malformation. The surgical operation was done the following day.

Postoperatively the patient noted progressively worsening shortness of breath. She did not com-

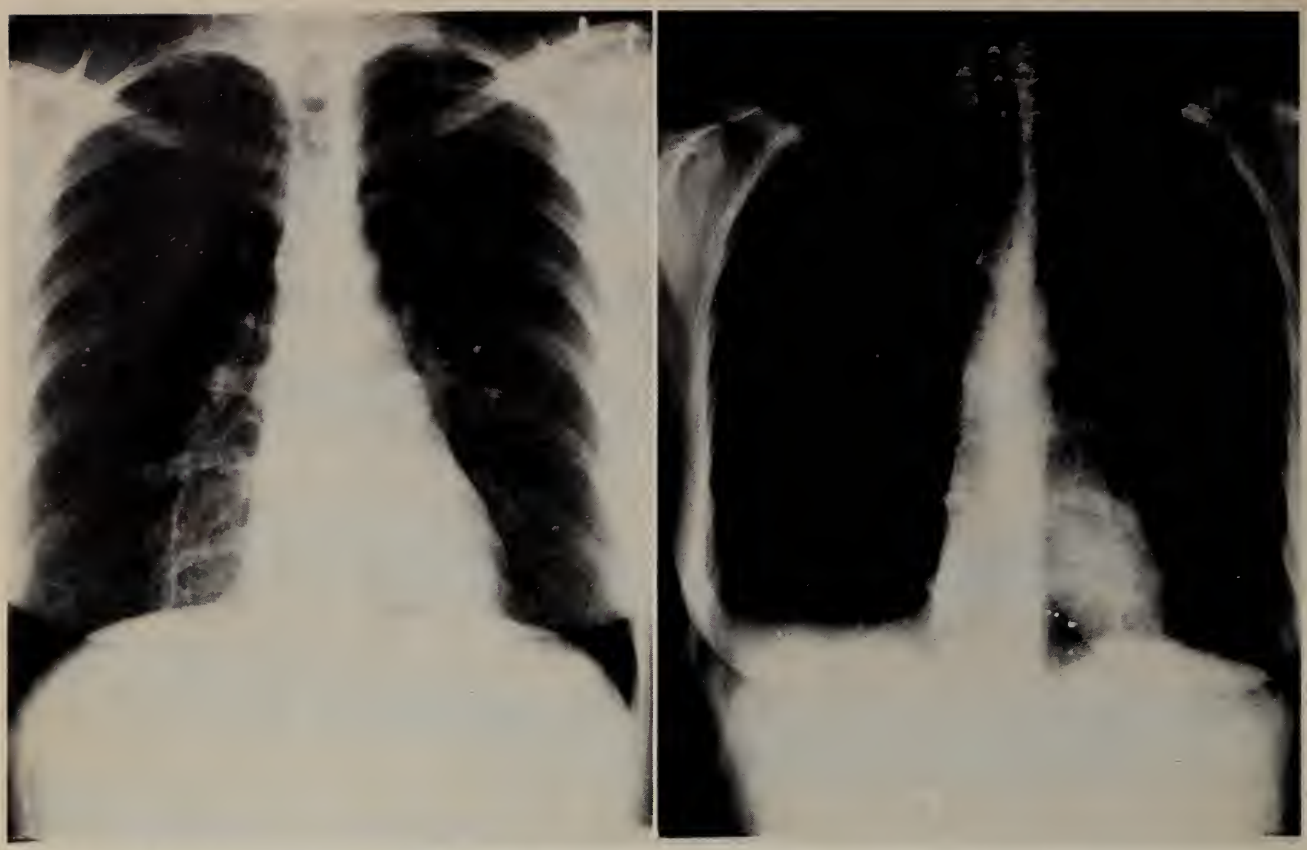


Figure 7.—**Left,** Posteroanterior chest radiograph before embolization shows a linear scar at the right base but is otherwise normal. **Right,** Posteroanterior chest radiograph after embolization shows multiple lead pellets at the lung bases and within the cardiac silhouette.

Figure 8.—On injection of contrast material into the lower aorta, a large mass of tortuous vessels in the pelvis with filling of a large abnormal venous channel is seen.

plain to any of the house officers or nurses because she was afraid it would interfere with her discharge plans. One month later a repeat angiogram was done and the A-V malformation had been completely removed.

Two weeks before admission she was seen in the emergency room for dyspnea, hemoptysis and substernal chest pain. On an x-ray film of the chest, bibasilar infiltrates, atelectasis and a left pleural effusion with hypoxia and hyperventilation were noted. These were thought to be the consequences of the lead balls which had errantly entered the pulmonary circulation when the embolization was done and were not thought to indicate a new disease process.

The patient was then discharged and seen two weeks later in the Arthritis Clinic where she was being followed for chronic low back pain. She there gave a history of sudden worsening of the shortness of breath two hours earlier. A lung scan was done and multiple subsegmental defects throughout both lung fields were noted.

The history of this patient illustrates some of the problems one has in diagnosing or suspecting pulmonary vascular disease. The patient related

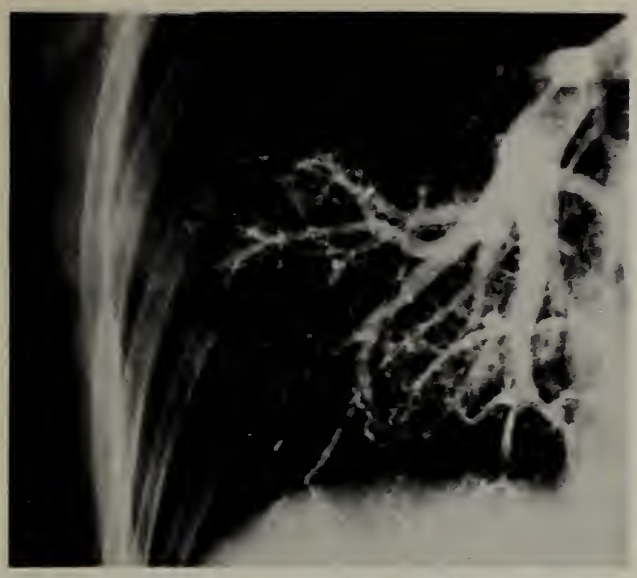


Figure 9.—Selective right inferior division pulmonary angiogram shows areas of avascularity at the right costophrenic angle. The small arteries are irregular with decreased numbers of side branches.

that she had had asthma since she was a child, and it had been severe enough to require occasional admissions to hospital. Since moving to California, however, she had no attacks of shortness of breath for 14 of the last 16 years. She did, however, smoke one to two packs of cigarettes per day and had an occasional cough. During the two years before admission, and this information was only obtained with a very careful history, she recalled that she had had episodic shortness of breath which she herself attributed to asthma but had not, in fact, been associated with wheezing. She had not sought the advice of a physician. The episodes of shortness of breath were on two occasions accompanied by hemoptysis. With some encouragement, she recalled that there had been swelling in the calves of her legs after prolonged sitting. The history gives us three possible reasons for episodes of shortness of breath: asthma, chronic bronchitis from smoking which worsened with viral infections and pulmonary vascular disease due to recurrent pulmonary emboli.

Results of preoperative pulmonary function studies done before the hysterectomy showed normal vital capacity, residual volume and total lung capacity within the normal range, completely normal diffusing capacity and normal FEV_1 as an absolute value and as a percentage of FVC. Findings on a single breath oxygen test, a test of gas distribution, were normal. The flow volume curve, which we believe to be a sensitive test of airway function, showed this function to be normal, and blood gases were consistent with acute hyperventilation. When the patient presented with shortness of breath at her most recent admission to hospital, repeat screening tests again showed only slight changes in volume, and although the diffusing capacity was within the normal range, it had fallen from the previous level. This might be consistent with multiple emboli. Again the forced vital capacity at one second was normal and findings on a single breath oxygen test were unremarkable. This case illustrates that in a patient with dyspnea normal or only slightly abnormal results on pulmonary function tests should make one think of the possibility of pulmonary vascular disease. Such findings are also consistent with asthma in remission, and the distinction must be made on clinical grounds or on further studies. Having seen these we asked Dr. Gamsu to do a pulmonary angiogram. He will review the films for us now.

Dr. Gamsu:* The chest film taken before the embolization is essentially normal (Figure 7). The film taken after embolization and before surgical operation shows a number of small lead pellets situated mainly at the lung bases. It was very interesting to note that the embolization was quite successful for in the pelvic arteriogram done before the embolization, large irregular venous or abnormal channels are shown (Figure 8). Following embolization and surgical operation, a repeat arteriogram showed no evidence of filling of any of these abnormal channels. In this case the embolization was successful, and these are extremely difficult to treat surgically without embolization. I do not want to give the impression that embolization under these circumstances is undertaken lightly. The complications are accepted and fully recognized. It was of interest to note that after the surgical operation, there was a pronounced increase in the number of lead balls seen in the lungs, and on the lateral film these are seen to lie probably in the myocardium of the right ventricle.

The pulmonary angiogram showed some interesting features (Figure 9). One is that we see no acute cutoffs, as might be seen with intraluminal clots, but we did see a number of areas in which there were no visible arterial branches. On the parenchymal phase, when the contrast material is in the small capillaries and small vessels, there was no visible vasculature in their regions. We were suspicious that some of the vessels showed evidence of chronic emboli which are difficult to

*Gordon Gamsu, MD, Assistant Professor of Radiology.

pick up angiographically, but one could see irregularities of the wall, representing incorporated emboli. So we have evidence here of possible small artery disease in the form of diffuse changes with pruning and irregularity of the small arteries. We have evidence of probable prior emboli as shown by the areas of avascularity and the irregularity within the arterial wall. One must remember that lead balls were not the only things which were embolized, so it is possible that some of the obstructions are the late aftereffects due to embolization of the other material which was put into the A-V malformation. We did not really confirm or exclude either recurrent emboli or underlying vascular disease by this study, but showed that both were probably present.

Dr. Boushey: Thank you very much Dr. Gamsu. On the basis of the history, I think we are inclined to agree that pulmonary emboli probably were present before the embolization procedure. I chose this case for presentation because it illustrates the kind of difficulties one can encounter if the diagnosis of multiple recurrent pulmonary emboli is not considered in a patient complaining of dyspnea. This was a particularly difficult case because the patient was reluctant to discuss symptoms with her physicians, possibly for fear of diagnostic intervention.

We believe that she had had recurrent pulmonary emboli for the two years before surgical operation and that the current symptoms are not only due to errant material that was introduced into the pelvic vessels, but to pulmonary emboli complicating surgical operation on the pelvis, a common occurrence. The patient is scheduled for exercise testing to obtain a baseline measurement of the current respiratory status to see if there is improvement with long-term anticoagulant therapy.

I would like to conclude by noting that multiple recurrent pulmonary emboli can occur in the absence of any history of phlebitis or of symptoms of pulmonary infarction. Dyspnea, particularly in the presence of normal or minimally abnormal pulmonary function studies, should lead to a more complete evaluation, not to the labeling of the patient as suffering from an anxiety neurosis, particularly if the dyspnea has been so severe as to cause the patient to alter his or her life style.

REFERENCES

1. Fishman AP: Dynamics of the pulmonary circulation, chap 48, *In* Handbook of Physiology—Vol 2, Section 2: Circulation. Washington, DC, American Physiol Soc, 1963, pp 1667-1743

2. Harris P, Heath D: The Human Pulmonary Circulation. Edinburgh, Livingstone, 1962

3. Nadel JA, Gold WM, Burgess JH: Early diagnosis of chronic pulmonary vascular obstruction. Am J Med 44:16-25, Jan 1968

4. Wessel HU, Kezdi P, Cugell DW: Respiratory and cardiovascular function in patients with severe pulmonary hypertension. Circulation 29:825-832, Jun 1964

5. Friedberg CK: Diseases of the Heart, 3rd Ed. Philadelphia, W B Saunders Co, 1966, p 1197

6. Stanek V, Widimsky J, Jebavy P: Respiratory function in recurrent pulmonary embolism. Respiration 30:223-233, Mar 1937

Important Advances in Clinical Medicine

Epitomes of Progress—Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Chest Diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Chest Diseases which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Office Pulmonary Function

THE EVALUATION of a patient with respiratory symptoms should include some measurement of pulmonary function. This is just as important as a blood count or electrocardiogram when the presenting problem is weakness, fatigue or chest pain.

Physiologically, the relationship of the volume of air exchanged by the lung to the amount of pressure required to distend the lung is known as compliance. This is a manifestation of the stiffness of the lung. Most pulmonary abnormalities causing symptomatic dyspnea are those related to loss of volume, or to changes in the static or dynamic properties of the lung.

Static changes or parynchymal structure abnormalities may make the lung stiff (decreased compliance). This is found in fibrosis or pneumonia. On the other hand, loss of elasticity (emphysema) produces increased compliance. Changes in dynamic forces are produced by airway obstruction, bronchospasm, secretions or loss of elasticity. The respiratory muscles must overcome these forces during breathing. Most diseases of the lungs exhibiting static or dynamic changes may be evaluated for functional changes initially in a physician's office.

Such pulmonary function tests are simple to carry out, are relatively inexpensive and require little time. It is important that a patient adequately understands the procedure and gives full cooperation. A wedge spirometer with a timing device will measure the volume and time the expiratory phase. These measurements correlate well with compliance and detect most pulmonary abnormalities, even in the early stages. Pulmonary function studies using this type of instrument include forced vital capacity (FVC), forced expiratory volumes at one or three seconds (FEV_1 or FEV_3), peak flow (usually at 200 to 1,200 ml of expiratory phase) and maximal midexpiratory flow (MMEF). A recorded spirogram expiratory curve (flow plotted against time) also allows for better interpretation of patient effort and for graphic reproducibility. FEV_1 and FEV/FVC ratio are probably the most frequently used measurements and correlate well

with the static and dynamic changes in the abnormal lung. Instruments such as a Vitalograph® or a Vitalor® are relatively inexpensive and quite adequate for such purposes. Recently, simple electronic devices with a digital printout have become available, but these usually do not have a recording spirometer.

Detected abnormalities may require more detailed pulmonary evaluation such as studies of diffusion, distribution of ventilation and perfusion, and arterial blood gas analysis for partial pressure of oxygen and of carbon dioxide (pO_2 and pCO_2) and for hydrogen ion concentration (pH). These are not usually routine office procedures.

Early detection of pulmonary disease and differential diagnosis of shortness of breath usually are begun in the physician's office and must include some form of pulmonary function evaluation. Routine checkups, insurance and industrial examinations, and preoperative and preemployment evaluations should include screening of pulmonary function. All persons who smoke should be given periodic evaluation of pulmonary reserve.

HOMER D. PEABODY, JR, MD

REFERENCES

Comroe HJ Jr, Nadel JA: Current Concepts: Screening tests of pulmonary function. N Engl J Med 282:1249-1253, May 1970

Peabody HD Jr: Office Management of Cigarette Cessation—Proceedings of the Second World Conference on Smoking and Health. September 1971, p 185

Nadel JA: Pulmonary Function Testing—Basics of R.D. American Thoracic Society, April 1973

Chester EH, Levine BE: Outlook 1974 Pulmonary. Patient Care, Jan 1, 1974

Bates DV: Prevention of emphysema. Chest 65:437-441, Apr 1974

New Beta Adrenergic Drugs in Asthma

RECENTLY, PHARMACOLOGISTS have modified the structure of the beta-1 bronchodilator isoproterenol so that enzymatic deactivation is minimized. These modifications have produced a whole class of new compounds, which not only are longer acting but whose effects upon several organs are vastly different. One of the major distinctions between these drugs—which include metaproterenol, terbutaline and salbutamol, and beta-1 agents—is that they produce less cardiac stimulation, while still retaining the ability to produce bronchodilatation; this type of response is termed beta-2. One of the major side effects of beta-2 drugs is muscle tremor; this manifestation of toxicity may be the limiting factor in many cases in treatment. However, there is evidence suggesting that muscle tremor but not bronchodilator activity tends to disappear with extended treatment (tolerance). In contrast to isoproterenol, which cannot be administered orally, these drugs are potentially available in all treatment usage forms: oral, injectable and inhalable as an aerosol (both liquid and pressurized). In comparison with the standard oral drug, ephedrine, which has multiple adrenergic activities (alpha and beta), beta-2 medications are longer acting and stimulate the heart less. Because of these properties, these beta-2 agents are now the adrenergic drugs of choice.

A. F. WILSON, MD, PH D

REFERENCES

Legge JS, Gaddie J, Palmer KNV: Comparison of two oral selective β_2-adrenergic stimulant drugs in bronchial asthma. Brit Med J 1:637, Mar 1971

Jack D: Selectively acting β-adrenoreceptor stimulants in asthma, *In* Austen KF, Lichtenstein LM (Eds): Asthma, Physiology, Immunopharmacology and Treatment. New York, Academic Press, 1973

Vineyard Sprayer's Lung

PERHAPS APPROPRIATE to California and other agricultural areas, T. G. Villar has reported on acute and chronic lung infiltrates due to Bordeaux mixture, a 1 to 2.5 percent solution of copper sulfate neutralized by hydrated lime, which is used as a pesticide. Other organocupric and organosulfurous preparations apparently can produce similar reactions. These pesticides are used to suppress mildew in vineyards, on farms, in parks, etc. These substances have only been widely used in recent years. Long periods of exposure are required, perhaps accounting for the paucity of reported cases so far.

After long exposure, histiocytic granulomata are produced containing copper, and fibrohyaline scars resulting may coalesce, liquefy and cavitate. Lesions histologically are similar to and may be confused with silicosis, but no doubly refractive particles are seen as in silicosis.

Asymptomatic forms may be clinically and in chest x-ray studies considered initially to be lung cancer. Acute forms with weakness; malaise; weight loss, and exudative, nodular or miliary infiltrates seen on an x-ray film of the chest may be mistaken for tuberculosis. Chronic forms with upper lobe infiltrates, dyspnea and restrictive ventilatory defects noted on pulmonary function testing may resemble silicosis, while others with diffuse lung infiltrates resemble chronic interstitial pulmonary fibrosis.

Some persons improve after cessation of ex-

posure; others remain asymptomatic, and later the condition begins to progress again. In many persons, the condition progresses gradually with formation of massive, upper lobe, bilateral lung opacities.

There is high incidence of lung cancer in vineyard workers using Bordeaux mixture. Vineyard sprayers' lung is best diagnosed by open or trephine lung biopsy; mediastinoscopy may prove to be helpful.

Preliminary inquiry showed that at least 340,000 pounds of copper compounds are used as agricultural pesticides in California each year. These consist of inorganic and organic copper compounds and mixtures.

OSCAR J. BALCHUM, MD, PH D

REFERENCES

Villar TG: Vineyard sprayer's lung. Am Rev Resp Dis 110:545-555, Nov 1974

Cortez J, Marques J: Vineyard sprayer's lung. Torax 24:415, 1969

Cortes J, Villar TG: Pulmonary Granulomatosis Due to Inhaled Particles—Proceedings International Pneumoconiosis Conference. Bucharest, Apimondia Publishing House, 1971, p 465

Evaluation and Treatment of a Solitary Lung Nodule

CONTROVERSY CONTINUES in the therapeutic management of noncalcified solitary lung nodules (6 cm or less). Diagnostic attempts are directed toward differentiating benign from malignant lesions, although malignancy is often suspected in 5 to 6 cm nodules. Definite diagnosis, short of operation, can not always be made; therefore, some authors studying this problem recommend the removal of all noncalcified coin lesions. Newer diagnostic techniques have aided evaluation before or instead of surgical procedures (small but definite rates of mortality and morbidity are associated with thoracotomy). With peripheral nodules, the incidence of carcinoma has been reported as being less than 20 percent when detection is the result of a routine x-ray film of the chest. A previous x-ray film of the chest for comparison is by far the most important diagnostic aid.

It is unusual for bronchogenic carcinoma to present as a solitary nodule in a patient under 35 years old. This fact may be in part attributable to the biological growth patterns of various carcinomas. It has been proposed that the doubling time—that is, the amount of time it takes the tumor to double its volume—is relatively constant and specific for certain lung neoplasms. Thus, the tumor which shows a twofold enlargement on x-ray studies has in fact increased in volume eightfold. The doubling time has been estimated as being between 30 and 300 days and when one sees a coin lesion that is 1 cm in diameter, it is proposed that 30 doublings have occurred. Squamous cell carcinoma has a much more rapid doubling time than an adenocarcinoma. Therefore, these neoplasms have probably been present from 8 to 16 years before their presence is shown on a chest x-ray film. This is not to minimize the importance of a work-up of a noncalcified solitary nodule in a patient under 35 years old, but merely to point out the slim chance that such a lesion will be malignant in nature.

Whereas evaluation of the solitary nodule in all age groups is similar, the major concern is directed toward those patients over 35 years old. Diagnostic procedures, in addition to following the plain chest x-ray studies and tomography (which serves to rule out the presence of calcium and to disclose any extension of tendrils into the lung substance), include a sputum examination for cytology and bronchial brush and bronchoscopic biopsies using a fiberoptic bronchoscope. These latter two are done under direct fluoroscopic vision preferably using biplain fluoroscopy so that one can get peripherally into the solitary nodule. These techniques are being improved continually by radiologists and respiratory disease physicans and such biopsy information will be highly important to a thoracic surgeon before an open-lung excisional biopsy.

Finally, the needle aspiration technique, again under fluoroscopic control, is useful in skilled hands. There is a low rate of morbidity associated with this technique, and better than 80 percent positive results have been recorded. It has been suggested that the risk of tumor implant along the needle tract is rare and therefore that this technique is less likely to spread malignant cells than with the potential for spillage of tumor cells during an open incisional biopsy. Again, if the surgeon knows beforehand that the lesion is malignant, he can carry out a closed procedure without doing a biopsy at the time of operation.

When there are negative findings from a needle biopsy or brush and bronchoscopic biopsies which

produce no material of diagnostic quality, a solitary lung nodule still must be considered potentially malignant. The patient's age and clinical situation will dictate if an open biopsy or interval x-ray studies of the chest alone will be necessary.

DAVID C. RAUSCH, MD

REFERENCES

Collins VP, Loeffler R, Tivey H, et al: Observations on growth rates of human tumors. Ann J Roentgenol Radium Ther Nucl Med 76:988-1000, Nov 1956

Jereb M, Sinner W: The use of some special radiologic procedures in chest disease. Radiol Clin North Am 11:109-123 Apr 1973

Steele JD: The Solitary Pulmonary Nodule. Springfield, Charles C Thomas, 1964

The Importance of 2,3-Diphosphoglycerate in Regulation of Tissue Oxygenation

THAT TISSUE OXYGENATION is dependent on more than just the arterial oxygen tension (PaO_2) and oxygen saturation is abundantly clear. The patient may have an excellent PaO_2 and oxygen (O_2) saturation, and yet have inadequate oxygenation at the tissue level due to a reduced hemoglobin (for example, reduced oxygen carrying capacity or O_2 content secondary to anemia). Oxygen delivery is as dependent on cardiac output as on O_2 content. The patient in shock may suffer from a tissue oxygen deficit due to inadequate tissue perfusion.

Another factor recognized many years ago is that the O_2 dissociation curve (relationship of O_2 saturation to PaO_2) may be shifted to the right or to the left. A shift of the curve to the right results in improved oxygen delivery by decreasing hemoglobin's affinity for O_2. A shift of the curve to the left increases hemoglobin's affinity for O_2 resulting in impaired O_2 release to the tissue. Those factors which shift the curve to the left include hypothermia, hypocapnia and alkalosis, while fever, hypercapnia and acidosis result in a rightward shift of the curve. Certain congenital hemoglobins may present with either increased or decreased affinity for oxygen.

A red cell phosphate enzyme, 2,3-diphosphoglycerate (2,3-DPG), has recently been shown to be an important factor regulating tissue O_2 delivery. An increased 2,3-DPG level decreases hemoglobin's affinity for O_2, resulting in improved release of O_2 at the tissue level. A reduction in 2,3-DPG has the opposite effect. Factors resulting in an increased 2,3-DPG include hypoxia, anemia and thyrotoxicosis. Blood preserved with acid citrate dextrose (ACD) preservative loses up to 50 percent of its 2,3-DPG within 72 hours. If this blood is transfused, the hemoglobin will not release O_2 to the tissue properly because the O_2 dissociation curve is shifted to the left, an effect lasting up to 24 hours. Citrate phosphate dextrose (CPD) preserved blood, however, maintains 2,3-DPG levels much more effectively for two to three weeks.

P_{50} is a term now being used to indicate if the O_2 dissociation curve is shifted. Normal P_{50} (the PaO_2 when the O_2 saturation is 50 percent) is approximately 26.5 mm of mercury. An increased P_{50} would indicate a shift of the curve to the right.

The patient-care team should take all of these factors into consideration when evaluating the adequacy of tissue oxygenation. For instance, correction of alkalosis in itself will improve O_2 delivery to the tissues.

JOHN E. HODGKIN, MD

REFERENCES

Finch CA, Lenfant C: Oxygen transport in man. N Engl J Med 286:407-415, Feb 1972

Klocke RA: Oxygen transport and 2,3-diphosphoglycerate (DPG). Chest 26:79-85, Nov 1972

Rifampin in the Treatment of Tuberculosis

RIFAMPIN (United States Adopted Name) or rifampicin (World Health Organization nonproprietary name) has proven to be a very effective addition to the list of antituberculosis agents. A semisynthetic derivative of an antibiotic recovered in 1957 by Italian researchers from a strain of Streptomyces mediterranei, rifampin has been shown to have a wide range of biologic activities in such diverse life forms as viruses, bacteria and mammals. When combined, isoniazid and rifampin have a remarkable ability to kill Mycobacterium tuberculosis, and to sterilize infected tissues in animal models. Trials in man have shown that the combination of isoniazid and rifampin is at least as effective as any previous combination of agents used, and has the added advantage of excellent patient tolerance. Rifampin in combination with other antituberculosis agents has proven highly effective in both short-course treatment

programs, and in intermittent (twice weekly) programs. Initial enthusiasm about rifampin has been tempered since experience indicates the occurrence of a variety of adverse reactions. Rifampin alters the metabolism of cortisol, oral contraceptives, bilirubin excretion and even rifampin itself. The intermittent use of rifampin has produced a variety of immunologic phenomena including cutaneous reactions, abdominal reactions, systemic flu-like reactions, respiratory reactions (primarily dyspnea and wheezing), purpura (with or without thrombocytopenia) and several instances of acute renal shutdown. The use of rifampin and isoniazid in daily regimens in a large United States Public Health Service study was associated with hepatic abnormalities in 12.4 percent of patients. These abnormalities, including frank hepatitis (3.5 percent), occurred throughout the entire period of combined drug administration. Considerable interest has been raised by observations that rifampin suppresses delayed hypersensitivity. Added to these adverse reactions is the cost of rifampin—nearly 200 times that of isoniazid. Therefore, it seems wise to restrict the use of rifampin at present to patients severely ill with tuberculosis, for retreatment or drug-resistant cases, short course regimens and for disease due to susceptible atypical mycobacterial organisms.

AUSTIN W. BREWIN, JR, MD

REFERENCES

Editorial: Rifampicin. Lancet 1:976-977, May 1969

Vall-Spinosa A, Lester TW: Rifampin—Characteristics and role in the chemotherapy of tuberculosis. Ann Int Med 74:758-760, May 1971

Aquinas M, Allan WG, Horsfall PA, et al: Adverse reactions to daily and intermittent rifampin regimens for pulmonary tuberculosis in Hong Kong. Br Med J 1:765-771, Mar 25, 1972

Isoniazid-rifampin for initial treatment of pulmonary tuberculosis—Preliminary report of a Public Health Service Cooperative Trial. May 1974, Personal Communication

Ruben FL, Winkelstein A, Fotiadis lG: Immunological responsiveness of tuberculosis patients receiving rifampin. Antimicrobial Agents and Chemotherapy 5:383-387, Apr 1974

Amphotericin for Coccidioidomycosis

WITH INCREASING EXPERIENCE in the use of amphotericin in both disseminated and progressive coccidioidomycosis, it has become apparent in recent years that the standard recommended doses for systemic use are unnecessarily high in many cases. It is usually not necessary to give more than a 1 gram course of the drug. This 1 gram total is best given in doses of 50 mg every day or every other day, following an initial period of gradually increasing dosages from 10 mg at the beginning to 50 mg for the fifth dose. With vigorous use of amphotericin administered locally whenever possible in meningitis, osteomyelitis, synovitis, pleural and peritoneal effusions and draining sinuses, a patient's morbidity and renal toxicity can be kept to a minimum. Surgical procedures can be scheduled within the 1 gram span to create an umbrella effect (that is, preoperative and postoperative administration of amphotericin). In the occasional case in which retreatment may be necessary, the above outlined principle would again apply with renal damage still being minimal.

HANS E. EINSTEIN, MD

REFERENCES

Utz JP, Kravetz HM, Einstein HE, et al: Chemotherapeutic agents for the pulmonary mycoses. Chest 60:260-262, Sep 1971

Upper Airway Obstruction

UPPER AIRWAY OBSTRUCTION due to the sequelae of intubation or tracheostomy is a potentially fatal lesion. Sudden death may occur even when the patient is in a hospital. Symptoms are not specific. Pronounced reduction in exercise tolerance, diffuse wheezing and paroxysmal dyspnea often occur before the telltale sign of stridor. Stridor is a late clinical sign and indicates the need for emergency surgical intervention.

Pulmonary function testing should be used in patients at risk of developing tracheal stenosis. A spirogram can be highly suggestive of upper airway obstruction. Both inspiratory and expiratory flow rates are decreased, but the former are reduced to a greater degree. The expiratory and inspiratory flow curves are nearly straight lines instead of the usual exponential curves (triangularization of the spirometry curve). The volumes expired in the first, second and third seconds are approximately equal. Also, maximum breathing capacity (MBC) is reduced more than would be expected on the basis of forced expiratory volume at one second (FEV_1). A final spirometric abnormality highly suggestive of upper airway obstruction is the shift in the baseline of the MBC tracing toward a lower lung volume which reflects the fact that more air leaves than enters the lung during this maneuver.

Fixed stenoses such as tracheal stricture and variable stenoses such as a paralyzed vocal cord can be differentiated with a high degree of accu-

racy using flow volume curves. A fixed lesion reflects itself in the flattening of both the inspiratory and expiratory flow volume loops; whereas a variable lesion produces only flattening of the inspiratory loop, leaving the expiratory loop fairly normal.

Since upper airway obstruction is potentially correctable by surgical operation, it is imperative that its presence be detected.

ROBERT E. HILLBERG, MD

REFERENCES

Spivey CJ Jr, Walsh RE, Perez-Guerra F, et al: Central airway obstruction—Report of seven cases. JAMA 226:1186-1189, Dec 1973

Shim C, Corro P, Park SS, et al: Pulmonary function studies in patients with upper airway obstruction. Am Rev Respir Dis 106: 233-238, Aug 1972

Hyatt RE, Black LF: The flow volume curve—A current perspective. Am Rev Respir Dis 107:191-199, Feb 1973

Exercise Training in the Treatment of Chronic Obstructive Lung Disease

THE LONG-TERM TREATMENT of patients with chronic obstructive lung disease (COLD) can be a frustrating experience at times. In spite of excellent medical care, little or no improvement in routine pulmonary function tests is shown. However, exercise training is one type of therapy producing evidence of definite objective improvement.

Exertional dyspnea and muscle fatigue are factors affecting and diminishing the "quality of life" for patients with moderately severe obstructive airway disease. In the past it has been common for a physician to advise a patient with COLD to limit his activity so that he does not do anything which would make him short of breath. The result of this advice is a more rapid deterioration in cardiopulmonary conditioning with the inevitable result of the patient having to remain at home.

An intensive exercise training program should be considered for every patient with COLD whose activities are limited by muscle weakness or shortness of breath. A program of this kind involves careful cardiopulmonary testing before starting exercise training with a treadmill or bicycle ergometer under the supervision of a physical therapist. After the initial training phase has been completed, a progressive exercise program at home is set up for the patient.

An exercise program of this kind has been shown to result in decreased resting and exercise heart rate, respiratory rate and minute ventilation; decreased oxygen consumption and carbon dioxide production during exercise; increased cardiac output with exercise; decreased lactate accumulation during exercise, and dramatic increase in the maximal work load tolerated. Patients who ordinarily would not be able to tolerate intensive exercise because of severe hypoxia or cardiac arrhythmia can have the benefit of this training by using supplemental oxygen during exercise.

An exercise training program should be a key part of any pulmonary rehabilitation plan. The improvement in physical fitness which results leads to a better quality of life for a patient with chronic obstructive lung disease.

JOHN E. HODGKIN, MD

REFERENCES

Pierce AK, Paez PN, Miller WF: Exercise testing with the aid of a portable oxygen supply in patients with emphysema. Am Rev Resp Dis 91:653-659, May 1965

Bass H, Whitcomb JF, Forman R: Exercise training: Therapy for patients with chronic obstructive pulmonary disease. Chest 57:116-121, 1970

ADVISORY PANEL TO THE SECTION ON CHEST DISEASES

HANS EINSTEIN, MD, *Chairman, Bakersfield*
CMA Scientific Board

WILBER HALLETT, MD
CMA Section on Chest Diseases
Chairman
Burbank

HURLEY L. MOTLEY, MD
CMA Section on Chest Diseases
Secretary
Los Angeles

JOHN HODGKIN, MD
Loma Linda University

STANLEY ROKAW, MD
CMA Section on Chest Diseases
Assistant Secretary
Los Angeles

ROBERT DE BUSK, MD
Stanford University

DAVID C. RAUSCH, MD
University of California, Davis

ARCHIE WILSON, MD
University of California, Irvine
California College of Medicine

DANIEL SIMMONS, MD
University of California, Los Angeles

KENNETH M. MOSERA MD
University of California, San Diego

WARREN GOLD, MD
University of California, San Francisco

OSCAR BALCHUM, MD
University of Southern California
Los Angeles

GEORGE G. BURTON, MD
Oakland

EDITORIALS

Malpractice and Social Change

In the current malpractice situation we are seeing what may be the first of many kinds of such crises in our society. The malpractice crisis of today may be only a forerunner of many others. Crises of this sort may well continue to occur until better methods can be found for people to live and work together in a complex society which is forever undergoing evolution and change, and where whatever is done in one situation can have truly profound and widespread effects throughout a significant segment of the whole.

It seems that three very basic realities of modern society have yet to become accommodated to one another. The first of these is our legal system, which enacts laws to solve problems and uses an adversary approach to interpret the laws and to resolve conflicts. At times this adversary approach may result in the issue being turned on legal points which are quite remote from the original problem which needed decision or resolution. For example, the doctrine of res ipsa loquitur may be applied in a malpractice suit in a situation where there was no real connection between what was presumed to be cause and what was presumed to be effect. Yet the doctrine holds that because they happened together or in sequence there must have been a connection.

The second basic reality is truth—as this is understood in science and human experience. In medicine, for example, the laws are those of science and human biology, and problems are solved and disputes are settled by recourse to what is known or can be found out through science and an examination of human experience and behavior as these are known to apply to the problem. Unfortunately this scientific approach has not yet reached the point where it can be used to solve all human problems and resolve all human disputes. But in any situation the truth always exists and it is what is sought and used by physicians in their practice and in disputes concerning medical science or patient care.

A third basic reality is the interdependence which has become a hallmark of today's world. The extent and meaning of this physical, social, economic and political interdependence is not yet fully understood or appreciated. Nor is either the legal system or science yet able to cope with it. Yet it is there and can be ignored only at peril. The professional liability problem, for instance, has developed from a series of precipitating incidents in separate areas of the nation. This came into sharp focus when one insurance company changed a contract for professional liability insurance for a group of physicians in Northern California. This action brought about a chain of events which may lead to a national crisis with as yet unknown implications for the fiscal viability of hospitals, for the availability of physicians' services and for further government intervention into the affairs of both the insurance industry and the practice of medicine.

For whatever reasons, medicine now finds itself at an interface where these disparate realities are coming together, and with some force at that. Understandably, things have begun to get a little rough and may become more so. But it seems likely that the role of physicians and of the medical profession is no different in this situation than in any other where patient care is involved. The interest of the patient comes first. Needed care must be available, its quality maintained and enhanced where possible, and any unnecessary costs for this care should be curtailed. These are the goals of the medical profession as it seeks essential reforms in this trying and unprecedented situation.

—MSMW

Medical Information for Travelers

ELSEWHERE in this issue of THE WESTERN JOURNAL OF MEDICINE, Dr. Elizabeth Barrett-Connor has written an excellent and useful "Advice to Travelers." More correctly, it is an advice to physicians who take care of patients who travel.

Since tourism is one of this country's major activities,* physicians can anticipate that sooner or later they will be confronted with patients seeking advice before travel and thereafter, particularly if diseases are acquired. In regard to the latter, it becomes necessary for physicians to become familiar with the manifestations of diseases not commonly seen in this country in order to assure prompt diagnosis and appropriate treatment.

Dr. Barrett-Connor's information on immunization requirements and source of vaccines is current and concise. In addition, she correctly points out some areas in which unanimity of opinion does not exist. Passive prophylaxis for viral hepatitis, Type A with immune serum globulin is one example where there are differing opinions. Many of the data cited by Dr. Barrett-Connor and others were derived from military experiences and suggest limited risk of hepatitis until after three to six months' sojourn in foreign lands. However, the military lifestyle varies considerably from civilian activities in many respects. Of great importance in this regard is that the military most frequently provides controlled food and water for its personnel, whereas the civilian "scrounges" off the land. Because of this, and other reasons, many physicians are more liberal in their use of immune serum globulin prophylaxis of hepatitis, even in patients whose anticipated exposure is less than three to six months, particularly when their travel bypasses ordinary tourist routes.

Another area where differences in opinion exist concerns tuberculosis. Most physicians in this country would *not* recommend immunization with Bacillus Calmette-Guerin (BCG) vaccine. A much preferred approach to this problem would be the reevaluation of patients with skin testing and chest x-ray studies at intervals after return from overseas.

Dr. Barrett-Connor has expressed the view that asymptomatic infection with Giardia does not require therapy. In an infection which may produce ill-defined and vague gastrointestinal and systemic complaints instead of classic diarrheal disease, it is too difficult to define "asymptomatic." In addition, the Giardia are always potential pathogens. For these reasons, I believe physicians should consider treatment.

Many of the data presented by Dr. Barrett-Connor and more, are summarized annually by the United States Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Atlanta, Georgia 30333. Physicians may obtain copies of this by contacting that agency (see Dr. Barrett-Connor's reference number 1).

LUCIEN B. GUZE, MD
Professor of Medicine
University of California, Los Angeles
Center for the Health Sciences
Chief of Staff for Research
VA Wadsworth Center, Los Angeles
Chief, Infections Diseases
Harbor General Hospital, Torrance

*According to data provided by the Passport Office of the U.S. Department of State (*Summary of Passport Statistics,* January 1975), there were 2,415,003 passports issued in 1974. Of these, 19 percent were issued to citizens living in the "Pacific Geographical Area," i.e., California, Washington, Hawaii, Oregon and Alaska. The "First Areas Designation" of these passport recipients were: Europe, 56 percent; Far East, 8 percent; North Central and South America, 21 percent; Middle East, 6 percent; Australia and Oceania, 7 percent and Africa, 2 percent. Fifty-one percent of passport recipients planned trips lasting up to one month and 11 percent planned trips for 1 to 2 months.

The Motivation and Conscience of the Physician

IN A RECENT EDITORIAL in *Science* (Changing climate for medicine. Science 188:975, Jun 6, 1975) Philip H. Abelson gives a masterly review of a "Changing Climate for Medicine." He calls attention once again to the fact that the essence of the practice of medicine is in the interaction between patient and physician. He notes that medicine will always remain an inexact science, that the best physicans are highly motivated and highly intuitive, and that much in patient care depends upon the motivation and conscience of the physician.

These are thoughts worth pondering at present, when approaches to the problems of health care are too often simplistic. Is it best to have highly motivated and conscientious physicians with relative freedom to use their knowledge, experience and, yes, their intuition, in the best interests of their patients? Or is it better to have a system of rules and restraints promulgated by various gov-

ernment agencies ruling upon what can or cannot be prescribed for what purpose, which operations are permissible under what circumstances and which are not, how long a patient may remain in a given type of health care facility with a given diagnosis and how many hours of formal continuing education a physician must have to keep his license to practice?

Would it not be much better—and much cheaper—for government and social policy to find ways to encourage and strengthen the motivation and conscience of the physician, rather than to force him into a defensive attitude where he must look upon both his patients and his government as potential enemies? After all, the attitude, motivation and conscience of physicians are essential, if not critical ingredients of both the cost and the quality of patient care. So far there is little evidence that government controls have done that much either to reduce costs or to improve quality. Maybe it is time for a more sophisticated approach.

—MSMW

Pulmonary Vascular Disease

PULMONARY EMBOLISM is a common problem often complicating the course of patients in hospital. The exact incidence is uncertain, but some studies suggest that the diagnosis may be missed in as many as 60 percent of patients dying on a general medical service. The natural history of pulmonary embolism is also uncertain, but the reported recurrence rate is as high as 20 to 40 percent in the first six months after a clinically-evident embolism. Does this recurrence rate decrease if the risk factor (such as congestive failure, contraceptive pills or long-bone factures) is eliminated? The answer to this question is critical to proper management, but data from appropriately controlled, prospective trials are not yet available.

Recurrent pulmonary embolism may present, often in relatively young, active persons, as dyspnea of unknown origin. This interesting, perplexing and theoretically preventable syndrome is elegantly reviewed in the Medical Staff Conference in this issue of THE WESTERN JOURNAL OF MEDICINE. The correct diagnosis depends on a high index of suspicion in the attending physician. If a patient has complaint of effort dyspnea (often episodic initially) that has caused a significant change of life style, a diagnosis of pulmonary embolism should be considered—particularly if none of the usual cardiopulmonary causes of dyspnea are present. Physicians should avoid attributing the dyspnea to psychoneurosis. In many patients psychoneurotic symptoms develop after being told repeatedly that "it's all in your head." Moreover, evidence of death of lung tissue, pulmonary hypertension, right ventricular enlargement and, finally, failure are all very late manifestations of this illness. A physician must not wait for these abnormalities to appear to confirm his suspicion.

Few physiological abnormalities may be present at rest, but an arterial blood sample usually will show evidence of chronic hyperventilation—decreased carbon dioxide partial pressure (PCO_2), decreased bicarbonate (HCO_3) and relatively normal hydrogen ion concentration (pH). This is a useful objective sign that the patient may have an abnormal ventilatory drive often associated with pulmonary vascular obstruction. Furthermore, although redistribution of blood flow may result in preservation of a normal carbon monoxide uptake, this is not the rule; in a series of 31 patients with documented chronic pulmonary vascular obstruction studied in our laboratory, diffusing capacity of the lung for carbon monoxide (DLCO) was decreased below 80 percent of predicted in 23 (mean DLCO: 11.8 ml/min X mmHg). DLCO can be measured quickly and noninvasively so it can be useful in screening patients in whom this diagnosis is suspected.

However, in most cases it will be necessary to evaluate these patients during exercise. During exercise, alveolar hyperventilation usually persists, arterial hypoxemia often develops, DLCO does not increase normally, while wasted ventilation increases to grossly abnormal levels, as more and more ventilation goes to poorly perfused alveoli. Pulmonary artery pressure increases to abnormal levels also, compared to that in healthy persons of comparable age, particularly when related to pulmonary blood flow.

The cause of the breathlessness in these unfortunate patients is unknown. It may be due to receptors in the walls of precapillary vessels which detect their abnormal distensibility, especially dur-

Dr. Gold's research is supported in part by U.S. Public Health Service grant HL 06285.

ing exercise when pulmonary arterial pulse pressure increases. Whatever the mechanism, experiments in animals and humans suggest that abnormal afferent signals are triggered in the vagus nerves by pulmonary vascular lesions. Mills and co-workers[1] reported that pulmonary embolism in rabbits increased firing rates in rapidly-adapting receptors innervated by single vagal nerve fibers. Gus and co-workers[2] showed that unilateral vagal blockade in patients with pulmonary vascular disease was associated with a decrease in hyperventilation and relief of dyspnea. If confirmed, these studies suggest possible therapeutic approaches to relieve dyspnea in such patients.

Future studies should clarify the natural history of the disease, particularly with respect to correction of risk factors; improve our methods of diagnosing occult venous disease as well as pulmonary embolism itself; and improve therapy, prophylactic as well as corrective.

WARREN M. GOLD, MD
Associate Professor
Department of Medicine
Cardiovascular Research Institute
University of California
San Francisco

REFERENCES

1. Mills JE, Sellick H, Widdicombe JG: Activity of lung irritant receptors in pulmonary microembolism, anaphylaxis and drug-induced bronchoconstriction. J Physiol (Lond) 203:337-357, Aug 1969
2. Guz A, Noble MIM, Eisele JH, et al: Experimental results of vagal block in cardiopulmonary disease, *In* Porter R (Ed): Breathing—Hering-Breur Centenary Symposium. London, J & A Churchill, 1970, pp 315-336

CASE REPORTS

Refer to: Kunkel FW, Neumann K, Scheinman MM: Runaway pacemaker—A serious and unresolved problem. West J Med 123:51-53, Jul 1975

Runaway Pacemaker

A Serious and Unresolved Problem

FREDERICK W. KUNKEL, MD
KURT NEUMANN, MD
MELVIN M. SCHEINMAN, MD
San Francisco

THE TREATMENT of certain cardiac arrhythmias with permanent intracardiac pacemakers is a widely used therapeutic modality. While technologic advances have increased the safety and effectiveness of these devices, serious complications still occur.[1-3] The purpose of this communication is to emphasize the continued importance and seriousness of pacemaker-induced ventricular tachycardia (runaway pacemaker).[4-7]

Reports of Cases

CASE 1. A 76-year-old man was brought to the emergency room at San Francisco General Hospital on January 17, 1973 in an unresponsive state. Four months before admission he had been evaluated at another hospital for prostatic carcinoma. During that admission, results of cardiac evaluation were unremarkable except for electrocardiographic findings, which showed sinus rhythm, a P-R interval of 0.20 seconds and right bundle branch block. One month before admission, the patient experienced postural lightheadness and dyspnea on exertion and on electrocardiogram showed complete A-V block with a ventricular response of 32 beats per minute. A permanent transvenous Cordis unipolar demand pacemaker (ECTOCOR catalogue No. 304-070, model 114c7) was implanted. There were no complications, and the patient's physician, who saw him weekly, noted a regular cardiac rhythm at a rate of 72 beats per minute.

On the morning of admission the patient was found unresponsive in the street, and resuscitative measures were initiated on route to the hospital. On physical examination the pulse and blood pressure were unobtainable, and the pupils were dilated and unresponsive. The initial rhythm electrocardiographic strip showed a pacemaker discharge rate of 270 beats per minute without ventricular response (Figure 1A). A chest incision was made and the pacing wire was disconnected from the implanted generator; the electrocardiographic tracing then showed a slow idioventricular rhythm (Figure 1B). A temporary external generator was connected to the existing electrode and electrical

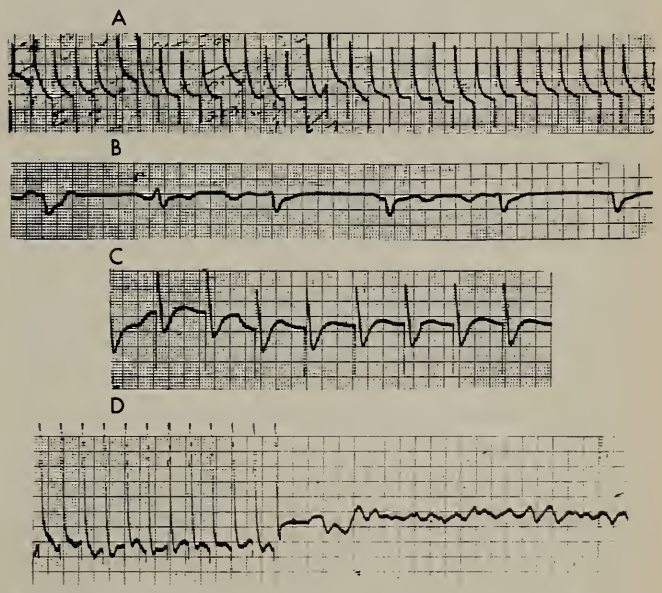


Figure 1.—(A-C) Electrocardiographic rhythm strips obtained in Case 1 show **(A)** a runaway pacemaker at a rate of 270 beats per minute, **(B)** idioventricular rhythm at a rate of approximately 40 beats per minute after disabling the malfunctioning pacemaker and **(C)** while pacing with an external pacemaker connected to the intracardiac electrode catheter. An electrocardiographic rhythm strip **(D)** obtained in Case 2 shows a runaway pacemaker with a discharge rate of 260 beats per minute; ventricular fibrillation occurred after the implanted pacemaker was disconnected.

From the Medical Service, San Francisco General Hospital, and the Department of Medicine and the Cardiovascular Research Institute, University of California, San Francisco.

This study was performed during tenure of the American Heart Association's Teaching Scholar Award to Dr. Scheinman.

Supported in part by grant No. HL 06285 from the National Institutes of Health, Bethesda, Maryland.

Submitted, revised, December 9, 1974.

Reprint requests to: M. M. Scheinman, MD, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110.

capture was accomplished (Figure 1C), but vital signs never returned.

On postmortem examination, left ventricular hypertrophy, extensive myocardial fibrosis and severe diffuse atherosclerotic coronary artery disease were seen. The pacemaker electrode tip was in place behind the anterior papillary muscle of the right ventricle with "no unusual fibrosis or tissue reaction." The generator was removed, exposed to room air for 72 hours, and connected to a Tektronix® oscilloscope and interval counter. The output of the generator was 6.5 millamperes (ma) when connected to a 500 ohm resistor. The pulse generator produced an impulse of normal contour and of 1.5 millisecond (msec) duration at a rate of 70 beats per minute.

Case 2. A 73-year-old man was brought to the emergency room at San Francisco General Hospital on June 12, 1974 in an unresponsive state with no vital signs. Six months before admission, a Cordis transvenous unipolar demand intracardiac pacemaker (Stanicor No. 143 E7-16663) was implanted at a rate of 72 beats per minute because of chronic congestive heart failure and complete A-V block. No complications occurred until the day of admission when, while shopping, the patient collapsed.

On admission, an electrocardiogram showed a pacemaker rate of 260 beats per minute (Figure 1D). The pacemaker generator was disconnected and an electrocardiogram showed ventricular fibrillation (Figure 1D). Resuscitative measures, including direct current cardioversion and attempts to pace the heart during periods of complete A-V block by an external pacemaker connected to the existing electrode catheter, were unsuccessful. Permission for postmortem examination could not be obtained, but the implanted generator was removed for further study. Daily oscillographic recordings of the generator output (as detailed previously) showed a gradual reduction in pacemaker rate until control implantation rate and normal wave form were achieved three days after exposure to air. The pacemaker was submerged in saline solution for 48 hours at 37°C (98.6°F); no change in form or rate of the generator impulse occurred.

Discussion

Pacemaker-induced ventricular tachycardia usually results from primary electronic component failure: defective capacitors, transistors, or transformers as well as leakage of biologic fluid into the generator box, which all may produce malfunction of the oscillator circuit, are believed to be important causes of component failure leading to a "runaway pacemaker."[8] In the cases reported here, the resumption of normal pacemaker function after exposure of the generators to air supports the concept of component failure (probably related to influx of tissue fluids) rather than primary generator malfunction. Immersion of the generator, extracted from the second patient, in saline solution for 48 hours failed, however, to produce an increased rate of pacemaker discharge.

Both pacemakers were returned to the manufacturer, but the precise cause of the malfunction still remains uncertain. In 1970, Wallace and coworkers[7] reviewed the 44 recorded instances of runaway pacemaker and found that this complication developed in pacemakers made by all of the major producers (and at all pacing modes) and was associated with a 34 percent mortality rate. Further improvements of pacemaker design have probably resulted in a decreased incidence of this complication; our search of the literature, for example, showed only one additional report of runaway pacemaker since 1970.[3] The present report is of importance because it emphasizes that the problem of pacemaker-induced ventricular tachycardia has not been resolved completely.

The runaway pacemaker complication poses important clinical problems because this complication may occur at any time (two days to 36 months)[9,10] after implantation and may occur without antecedent change in pacemaker discharge rate or sensing function, or change in the generator impulse wave form. The increased rate is associated with diminished generator output, which may or may not result in ventricular capture. In either event, emergency treatment dictates either prompt disabling of the generator and control of the heart rate with preferably an external pacemaker connected to the original intracardiac electrode or infusion of isoproterenol.

Summary

Two patients with implanted permanent transvenous pacemakers had cardiac arrests associated with very rapid pacemaker discharge rates (runaway pacemaker). This complication developed without other evidence of pacemaker failure four months after insertion in one patient and six months after insertion in the other. Both patients died. Exposure of the batteries to room air after 48 hours resulted in return of normal pacing

function. This report documents the persistence and seriousness of this condition and emphasizes the need for prompt recognition and treatment of this emergency.

ADDENDUM: Both batteries were returned to the manufacturer but we have not as yet received the technical analyses of the failed units. Since submission of this manuscript, one additional report of runaway pacemaker associated with a fatal outcome has been published.[11]

ACKNOWLEDGMENTS: We gratefully acknowledge the clinical information sent to us by Dr. Vernon C. Harp, Jr. for Case No. 1 and to Dr. Frank Solomon for data in Case No. 2.

REFERENCES

1. Kosowsky BD, Barr I: Complications and malfunctions of electrical cardiac pacemakers. Progr Cardiovasc Dis 14:501-514, 1972

2. Chung EK: Cardiac arrhythmias related to artificial pacemakers. J Electrocardiol 4:220-226, 1971

3. Conklin EF, Gregory J, Grace WJ, et al: Use of the permanent transvenous pacemaker in 168 consecutive patients. Am Heart J 82:4-15, 1971

4. Harris RS Jr, Becker DJ, Rodensky PL, et al: Symptomatic paroxysmal pacemaker-induced ventricular tachycardia. Am J Cardiol 11:403-408, 1963

5. Wisoff BG, Gabor GE, Donoso E: Pacemaker-induced ventricular tachycardia. JAMA 192:258-259, 1965

6. Aldridge HE, Kahn O: An unusual hazard of fixed-rate cardiac pacemakers. Canad Med Ass J 93:95-97, 1965

7. Wallace WA, Abelmann WH, Norman JC: Runaway demand pacemaker—Report, in vitro reproduction, and review. Ann Thorac Surg 9:209-220, 1970

8. Furman S, Escher DJW, Lister J, et al: A comprehensive schema for management of pacemaker malfunction. Ann Surg 163: 611-620, 1966

9. Nathan DA, Samet P, Center S, et al: Long term correction of complete heart block—Clinical and physiologic studies of a new type of implantable synchronous pacer. Progr Cardiovasc Dis 6:538-565, 1964

10. Hellerstein HK, Hornsten TR, Ankeney JL: The runaway artificial pacemaker—Report of a case. Ohio Med J 62:907-911, 1966

11. Bramowitz AD, Smith JW, Eber LM, et al: Runaway pacemaker—A persisting problem. JAMA 228:340-341, 1974

Refer to: Vieweg WVR, Tretheway DG: Transmural myocardial infarction in a young man with normal coronary arteriograms. West J Med 123:53-55, Jul 1975

Transmural Myocardial Infarction in a Young Man with Normal Coronary Arteriograms

W. V. R. VIEWEG, CDR, MC, USN
D. G. TRETHEWAY, LCDR, MC, USN
San Diego

WOMEN SEEM particularly predisposed to angina pectoris and subendocardial infarction without demonstrable coronary artery disease.[1,2] Rarely has a transmural infarction occurred in a young man without other cardiac disease or apparent cause as is described in this report.

Report of a Case

A 29-year-old Navy man was admitted to the hospital because of crushing retrosternal pain associated with shortness of breath and diaphoresis. There was no history of prior chest pain, high blood pressure or lipid disturbance, and no family history of coronary artery disease. Findings on the initial electrocardiogram showed an acute inferolateral transmural myocardial infarction (Figure 1a). Daily serum glutamic oxaloacetic transaminase determinations were 29, 320, 118, 55 and 66 milliunits (mU) per millimeter with a normal range of 7 to 40. The patient's course was uncomplicated.

Two months after infarction, an electrocardio-

From the Cardiology Branch, Department of Medicine; and the Clinical Investigation Center, Naval Regional Medical Center, San Diego.

Submitted, revised, January 14, 1975.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or the naval service at large.

Reprint requests to W. V. R. Vieweg, CDR, MC, USN. Cardiology Branch, Department of Medicine, Naval Regional Medical Center, San Diego, CA 92134.

gram showed persistent Q-waves and T-wave inversion in the inferolateral leads (Figure 1b). The patient was exercised on a treadmill to 92 percent of predicted maximum heart rate (175 beats per minute). Chest pain did not develop and there were no diagnostic postexercise electrocardiographic changes noted. At this time, cardiac catheterization and selective coronary arteriography were carried out. The left ventricular end diastolic pressure was 13 at rest and rose to 18 mm of mercury after a left ventriculogram was made. On the left ventriculogram, akinesis of the inferior wall was noted. The ejection fraction was 62 percent and no mitral regurgitation was noted (Figure 2). Selective coronary arteriograms were of excellent quality and showed a dominant right circulation. Findings on coronary arteriograms were entirely normal (Figure 3).

Discussion

Obstructive atherosclerotic coronary artery lesions are present in the vast majority of patients who have sustained a myocardial infarction. Sources of nonatherosclerotic obstructive coronary lesions include aortic cusp polyp,[3] thrombus, embolus, spasm,[4] vasculitis, dissecting aortic aneurysm and luetic occlusion of the coronary ostia. Nonobstructive causes include abnormal hemoglobin-oxygen dissociation,[1] congenital coronary artery anatomic variations and low cardiac output states. Since 1967[2] many articles have appeared describing an apparent paradox of angina pectoris or myocardial infarction and normal coronary arteries. In contrast to the usual population with symptomatic coronary atherosclerosis, many of these patients are women and, not infrequently, they have received oral contraceptive agents.[5,6]

In addition to the present case, eight well-documented cases of men under the age of 30 years were found in the literature who had had an acute transmural myocardial infarction and were subsequently shown to have normal coronary arteries by means of selective coronary arteriography.[7-12] In each instance there was no obvious cause for the infarction. Findings on left ventriculograms were abnormal except in the case of Nizet and Robertson involving a 17-year-old man.[7] The explanation most readily offered to account for

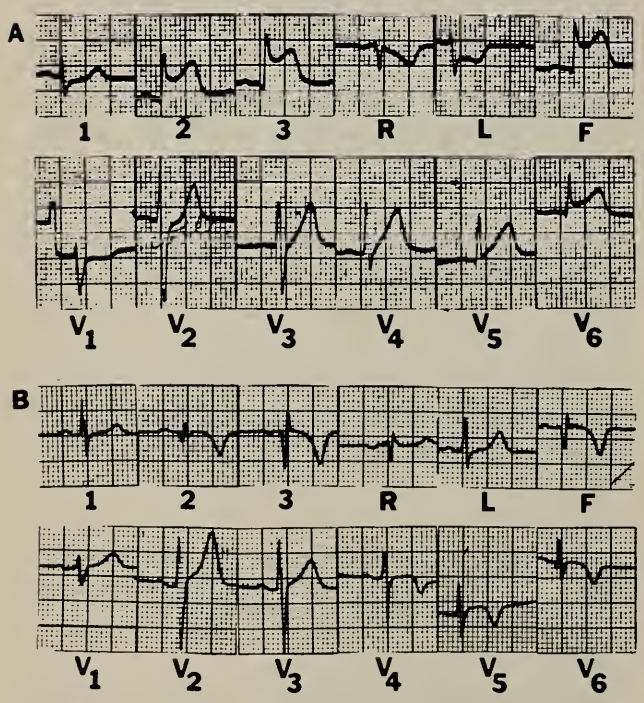


Figure 1.—**A,** Acute inferolateral transmural myocardial infarction. **B,** persistent Q-waves and T-wave inversion in the inferolateral leads two months after infarction.

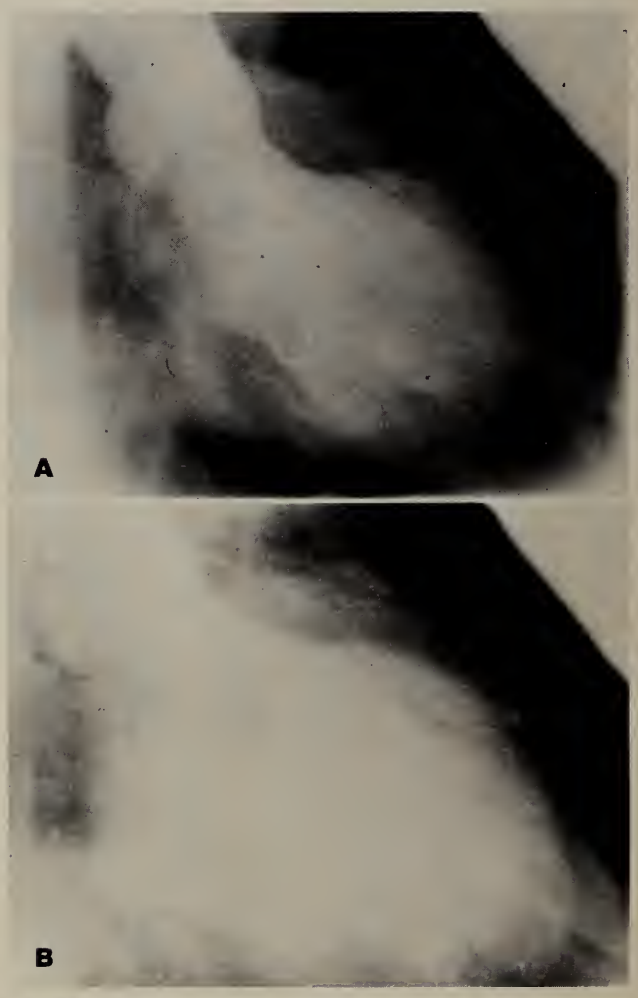


Figure 2.—Left ventriculogram in 30° right anterior oblique projection: **A,** systole and **B,** diastole. The ejection fraction was 62 percent. There was inferior wall akinesis.

the myocardial infarction was that of coronary artery thrombosis or embolism with subsequent recanalization. Such an event has been documented by serial selective coronary arteriography.[5,8] If this accounted for the myocardial infarction in the present case then the recanalization process can be completed in as short a period as two months.

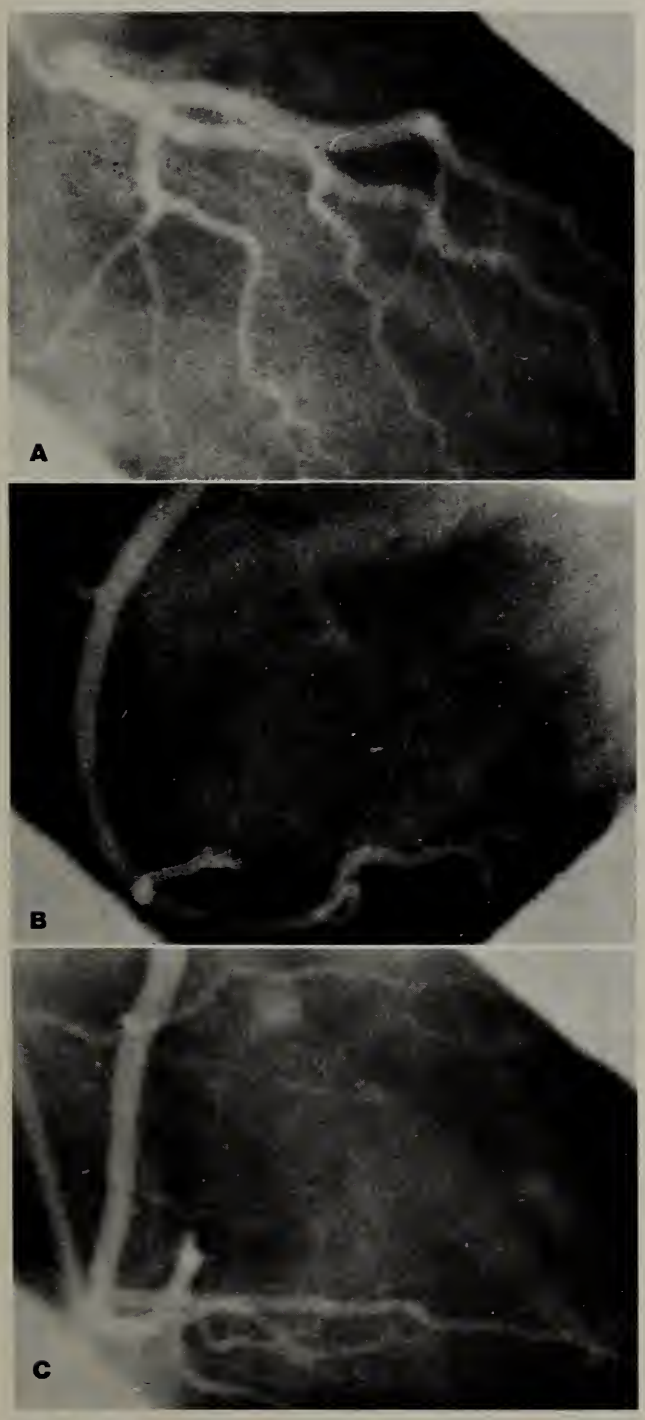


Figure 3.—**A,** normal left coronary artery in right anterior oblique projection. **B,** normal right coronary artery in left anterior oblique and **C,** right anterior oblique projections.

Since the coronary arteries are normal in the cases under discussion the prognosis should be related to residual left ventricular function. In the present case the outlook should be favorable since the ejection fraction was 62 percent in the face of inferior wall hypokinesis. In addition, excellent exercise tolerance was shown at the time of treadmill examination.

Recently Khan and Haywood reported a 12 percent incidence (9 of 78 patients) of "normal or near normal coronary arteries" in patients who had had an acute transmural myocardial infarction.[13] Two of the nine patients were under 30 years of age. Many patients are seen at the Naval Regional Medical Center, San Diego, California who have had an acute myocardial infarction before the age of 30 years. In such patients, selective coronary arteriography routinely is used in order to establish prognosis. Over the past three years (1972 to 1974) only one other patient was found who had had an acute myocardial infarction and subsequently was shown to have normal findings on coronary arteriograms.[14]

REFERENCES

1. Eliot RS, Bratt G: The paradox of myocardial ischemia and necrosis in young women with normal coronary arteriograms—Relation to abnormal hemoglobin-oxygen dissociation. Am J Cardiol 23:633-638, 1969

2. Likoff W, Segal BL, Kasparian H: Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. N Engl J Med 276:1063-1066, 1967

3. Butterworth JS, Poindexter CA: Papilloma of cusp of the aortic valve—Report of a patient with sudden death. Circulation 48:213-215, 1973

4. Cheng TO, Bashour T, Singh BK, et al: Myocardial infarction in the absence of coronary arteriosclerosis—Result of coronary spasm (?). Am J Cardiol 30:680-682, 1972

5. Glancy DL, Marcus ML, Epstein SE: Myocardial infarction in young women with normal coronary arteriograms. Circulation 44:495-502, 1971

6. Henderson RR, Hansing CE, Razavi M, et al: Resolution of an obstructive coronary lesion as demonstrated by selective angiography in a patient with transmural myocardial infarction. Am J Cardiol 31:785-788, 1973

7. Nizet PM, Robertson L: Normal coronary arteriogram following myocardial infarction in a 17-year-old boy. Am J Cardiol 28:715-717, 1971

8. Bruschke AVG, Bruyneel KJJ, Bloch A, et al: Acute myocardial infarction without obstructive coronary artery disease demonstrated by selective cinearteriography. Br Heart J 33:585-594, 1971

9. Kimbiris D, Segal BL, Munir M, et al: Myocardial infarction in patients with normal patent coronary arteries as visualized by cinearteriography. Am J Cardiol 29:724-728, 1972

10. Sidd JJ, Kemp HG, Gorlin R: Acute myocardial infarction in a 19-year-old student in the absence of coronary artery disease. N Engl J Med 282:1306-1307, 1970

11. Campeau L, Lesperance J, Bourassa MG, et al: Myocardial infarction without obstructive disease at coronary arteriography. Can Med Assoc J 99:837-843, 1968

12. Potts KH, Stein PD, Houk PC: Transmural myocardial infarction with arteriographically normal appearing coronary arteries. Chest 62:549-552, 1972

13. Khan AH, Haywood LJ: Myocardial infarction in nine patients with radiographically patent coronary arteries. N Engl J Med 291:427-431, 1974

14. Smith DC, Vieweg WVR: Acute transmural myocardial infarction—Its occurrence in a young man without demonstrable coronary artery disease. JAMA 229:811-813, 1974

Refer to: Weinstein EC: Mondor's disease. West J Med 123:56-57, Jul 1975

Mondor's Disease

EUGENE C. WEINSTEIN, MD
Van Nuys, California

CARCINOMA OF THE BREAST, the leading cause of death among women, is receiving ever increasing attention in both the medical literature and the lay press. Arguments concerning its treatment can be found in abundance, but its clinical diagnosis is not given the attention it warrants. The most fearful event that can befall a woman is the discovery of a breast mass. She visits her physician with foreboding and assumes she has cancer before entering his office. One of the greatest gifts the physician can bestow upon his patient is the reassurance that the mass in question is not malignant.

Mondor's disease, a sclerosing thrombophlebitis of the veins of the chest wall, is a disease entity which can be diagnosed clinically and requires only symptomatic therapy. However, in order to properly diagnose this disease state, a physician must be aware of its existence and its clinicopathologic course.

The first report of a case of thrombophlebitis of the thoracoepigastric veins was made by Fagge in 1869.[1] However, it was not until 1939, when Henri Mondor[2] presented four cases with a discussion of the clinicopathologic process, that the understanding of the disease was placed on a firm foundation. Subsequent reports by Adair,[3] Mondor and Bertrand,[4] Farrow[5] and Bucher[6] helped clarify the process until at present the disease is a well-recognized entity.

The following study was prompted by the recent opportunity to treat two patients with Mondor's disease. Its purpose is to familiarize all practicing physicians with this interesting disease entity.

Reports of Cases

CASE 1. A 47-year-old woman with known severe fibrocystic disease of both breasts was seen with a complaint of a one-day history of a tender mass in the upper outer quadrant of the left breast. There was no history of recent surgical operation, infection or trauma.

On physical examination, the patient was seen to have extensive bilateral fibrocystic disease; however, in the symptomatic area there was an oblong tender mass which was easily seen with the left arm raised. A diagnosis of thrombophlebitis of the lateral thoracic vein, in an acute stage, was made, and the patient was treated with analgesics, moist heat and reassurance. When reexamined one month later, the mass had completely resolved.

CASE 2. A 23-year-old woman noted a sore, bruised area on the outer aspect of the right breast three weeks before being seen. One day before examination, the patient noticed a firm cord in the involved area. There was no history of infection, trauma or recent surgical operation.

On examination, with the patient's hands at her side, no obvious mass was noted. However, when the right arm was raised, a firm fibrous cord along the course of the lateral thoracic vein was both seen and palpated. There was no acute inflammation present at this time and consequently reassurance to the patient as to the nature of the problem was all that was required.

Clinico-Pathologic Characteristics

Mondor's disease occurs three times as frequently in women as in men, and most patients have been in the age range of 30 to 60 years old. However, as can be seen by the second case reported here and the report by Camiel and Benninghoff,[7] it is also found in women in their twenties.

The most prominent clinical feature is the sud-

From the Department of Surgery, Ross-Loos Medical Group, Van Nuys.

Submitted October 29, 1974.

Reprint requests to: E. C. Weinstein, MD, Department of Surgery, Ross-Loos Medical Group, 6844 Sepulveda Boulevard, Van Nuys, CA 91405.

den appearance of a cord-like thrombosed vein which is at first red and tender and subsequently changes into a painless, tough fibrous band. The patient's attention is usually called to the involved area by the pain, movement tending to accentuate the discomfort. There are no systemic symptoms, and if a biopsy specimen of the involved area is taken at this time it will show an acute thrombophlebitis with thrombus formation. Both sides of the breast have an equal incidence of involvement.

If the patient does not seek medical attention at this time, the tenderness will gradually disappear while the thrombus undergoes organization and eventually recanalization of the vein. In the end stage of the disease process, a thick-walled vein remains which, on clinical examination, has a hard rope-like appearance and on occasion may result in a furrowing of the breast.[8]

The veins involved are the lateral thoracic, thoracoepigastric and the superior epigastric; therefore the upper and inner portions of the breast or chest wall can never be involved by the disease process.

Cause

As in most entities where the exact causative agent is not known, there are many theories as to the initiating factor. The factors reportedly involved include tight-fitting dresses and tight bras, shaving of the axilla, infections, blood dyscrasias, suppurative sebaceous cysts and hidradenitis suppurativa.

Skipworth and associates[9] reported a case associated with lupus erythematosus, while Hermann,[10] in a comprehensive article, reported four cases occurring after operative procedures. In his review, he reported five cases as of idiopathic origin and noted that most of the cases occurring after operative procedures were in postmenopausal patients while the majority of the idiopathic cases occurred in menstruating patients.

Diagnosis and Treatment

The two disease entities most likely to be confused with Mondor's disease are breast abscess and inflammatory carcinoma. The differential diagnosis can be made if one considers the sudden onset of Mondor's disease, its location and the physical findings of a localized process restricted to a palpable vein.

The treatment is entirely symptomatic and consists of hot, wet dressings and anodynes for relief of pain. Other recommended treatment modalities have included enzymes, corticosteroids, antibiotics, vaccines and anticoagulants. However, none of the latter modalities have been proven to hasten the resolution of the pathologic process.

The disease process runs its course in from three weeks to six months. Therefore, the major benefit the physician can provide his patient is reassurance.

Conclusion

Mondor's disease is a localized thrombophlebitis of the veins of the thoracoepigastric area. It is clinically recognized by its localization to a definable venous channel and may be recognized in its acute or phlebitic stage or in its chronic or fibrotic stage. Its importance is that it must be differentiated from an inflammatory breast carcinoma in the early stage and a scirrhous carcinoma in the late stage. The treatment is symptomatic and includes reassurance to the patient as to the exact nature of the process.

Summary

Thrombophlebitis of the thoracoepigastric veins may be mistaken for carcinoma of the breast. An understanding of the pathology involved in this form of sclerosing phlebitis will enable a correct diagnosis to be made and appropriate reassurance to be given.

REFERENCES

1. Fagge CH (quoted by Hermann JB): Thrombophlebitis of breast and contiguous thoracoabdominal wall (Mondor's disease). NY State J Med 66:3146-3152, Dec 15, 1966

2. Mondor H (quoted by Hogan GF): Mondor's disease. Arch Intern Med 113:881-885, Jun 1964

3. Adair FE: Cancer of the breast. Practitioner 165:473-481, Nov 1950

4. Mondor H, Bertrand I: Thrombo-phlebitis et periphlebitis de la paroi thoracique anterieure. LaPresse Med 55:1533-1535, Nov 21, 1951

5. Farrow JH: Thrombophlebitis of the superficial veins of the breast and anterior chest wall (Mondor's disease). Surg Gynec Obstet 101:63-68, Jul 1955

6. Bucher J, Schirger A, Clagett OT, et al: Mondor's disease—A vascular rarity. Proc Staff Mtgs Mayo Clinic 37:651-656, Dec 5, 1962

7. Camiel MR, Benninghoff DL: Mondor's disease in the breast. J Natl Med Assn 63:352-353, Sep 1971

8. Hogan GF: Mondor's disease. Arch Intern Med 113:881-885, Jun 1964

9. Skipworth GB, Morris JB, Goldstein N: Bilateral Mondor's disease. Arch Derm 95:95-97, Jan 1967

10. Hermann JB: Thrombophlebitis of breast and contiguous thoracoabdominal wall (Mondor's disease). NY State J Med 66:3146-3152, Dec 15, 1966

Refer to: Gilliland BC, Caldwell JH: A splash in the joint. West J Med 123:58-59, Jul 1975

A Splash in the Joint

BRUCE C. GILLILAND, MD
JAMES H. CALDWELL, MD
Seattle

SEPTIC ARTHRITIS is usually characterized by the acute onset of pain, swelling and redness involving one or a few joints and is often accompanied by fever and chills.[1] The typical signs of joint inflammation, however, may be masked in patients receiving corticosteroids or immunosuppressive drugs, or in patients with an overwhelming generalized illness. A patient on corticosteroids and without obvious manifestations of acute articular inflammation is presented to call attention to an interesting physical finding, which in most circumstances is diagnostic of septic arthritis.

Report of a Case

A 68-year old white woman was admitted to a local hospital because of leg weakness. Physical examination on admission was described as being within normal limits except for blood pressure of 180/100 mm of mercury and massive obesity. During the stay in hospital, there were several episodes of fever, confusion and hypertension. Findings on brain and liver scans, x-ray films of the chest and intravenous pyelography were reported as normal; blood cultures were negative. The patient refused to walk because of bilateral knee pain. On the 31st hospital day, administration of prednisone (50 mg per day) was begun for treatment of possible collagen-vascular disease. On the 45th hospital day, a urinary tract infection was noted. Urine cultures grew Escherichia coli and pseudomonas for which ampicillin, cephalexin and cloxacillin were given for ten days. After two months, the patient was transferred to the University of Washington Hospital because of increasing stupor.

On examination at admission, the patient was seen to be obese and confused, and was able to answer only a few questions. Blood pressure was 110/72 mm of mercury, the temperature 38.8°C (101.8°F) and the pulse rate 106 beats per min. The skin turgor was poor. Decubital ulcers were present over the right foot, left malleolus and buttocks. Chest and heart were within normal limits. Babinski sign was present and the deep tendon reflexes were absent. Knees were slightly swollen and tender on palpation; erythema and warmth were absent. Crepitus and pain occurred with flexion. Results of laboratory tests were: hematocrit 35, leukocyte count 16,500 per cu mm with a shift to the left, erythrocyte sedimentation rate 55 mm per hr (Westergren), platelet count 37,000 per cu mm, electrolytes were normal, blood urea nitrogen (BUN) 132 mg per 100 ml, creatinine 3.0 mg per 100 ml. The patient was considered to be in renal failure complicated by saline depletion. The joint findings were initially attributed to osteoarthritis. Urine culture grew E coli and Proteus mirabilis; skin lesions grew E coli. Administration of cephalosporin and kanamycin was begun.

When the patient was seen by the rheumatology service on the third hospital day, both

Figure 1.—Lateral view of left knee showing large gas shadow in suprapatellar pouch. Gas is also observed posteriorly in fascial plane.

From the Department of Medicine, Division of Rheumatology, University of Washington School of Medicine.

Submitted October 11, 1974.

Reprint requests to: B. C. Gilliland, MD, Department of Medicine, Division of Rheumatology, RG-20, University of Washington School of Medicine, Seattle, WA 98195.

knees were swollen, tender on palpation and slightly warm, but not erythematous. On gentle shaking of each leg, a splashing sound was generated in the knee, audible across the room. On radiographs of the knees, gas in the joint space and suprapatellar bursa was seen (see Figure 1). Gas was also seen extending up the fascial planes of the thighs. Narrowing of the joint space, subchondral sclerosis, and osteophytes at joint margins indicated underlying osteoarthritis. No bone erosions or evidence of osteomyelitis were present. Aspiration of the knees yielded grossly purulent material which grew E coli, as did the blood culture taken the previous day. Later that day the patient went into septic shock and, despite appropriate antibiotics and supportive measures, died on the fifth hospital day.

Discussion

Septic arthritis was initially overlooked in this patient due to the overwhelming nature of illness, and because signs of acute joint inflammation were minimal due to corticosteroid therapy and the generalized debilitated condition. Tenderness, crepitus and swelling of the knees were therefore attributed to osteoarthritis. However, when an audible "splash" sound in the knees was noted, the diagnosis of septic arthritis due to a gas-forming microorganism was immediately considered. Gas in the joint was subsequently confirmed radiographically, and aspiration of the joint yielded grossly purulent material which showed Gram-negative rods and grew E coli on culture.

The splash sign has not been previously stressed as a sign of septic arthritis due to gas-forming microorganisms such as E coli or clostridia. This sound was not heard during routine palpation of the joint; it required shaking or quickly rocking the leg back and forth. Rapid alternating ballottement of opposite sides of the knee joint also produced the sound. An audible splash cannot be produced with intrasynovial fluid alone but requires the presence of an air-fluid interface. It is therefore comparable to the well known succussion splash observed in patients with pneumothorax or gastric outlet obstruction. The only other explanation for an air-fluid level and a possible "splash" sign in a joint is the prior introduction of air during aspiration of the joint or for air-contrast radiography.

Septic arthritis due to Gram-negative bacilli is uncommon, representing less than 5 percent of the reported pyogenic joint infections.[1] The clinical setting commonly found in patients with this type of septic arthritis and present in our patient includes the existence of an underlying chronic debilitating illness, concurrent extra-articular infection especially of the urinary tract or gall bladder and immunosuppressive or corticosteroid therapy. Previously damaged joint or joints are often selected as the site for the hematogenous spread of infection. Mortality is high; contractures, ankylosis and osteomyelitis are common sequellae of this type of infection.[2]

Septic arthritis is a medical emergency. Immediate aspiration with aerobic and anaerobic cultures is indicated on any joint suspected of being infected, especially in the compromised host. Radiographs of the affected joint are not diagnostic early in the course of acute septic arthritis except when gas is present. Prompt recognition and early treatment of septic arthritis are very important for preventing permanent joint damage and eliminating sources for continued septicemia.

REFERENCES

1. Schmid FR: Principles of diagnosis and treatment of infectious arthritis, chap 63, *In* Hollander JL, McCarty DJ (Eds): Arthritis and Allied Conditions, 8th Ed. Philadelphia, Lea and Febiger, 1972, pp 1203-1217

2. Goldenberg DL, Brandt KN, Cathcart ES, et al: Acute arthritis caused by Gram-negative bacilli—A clinical characterization. Medicine 53:197-208, 1974

LETTERS *to the Editor*

Cancer Immunotherapy: A Word of Caution About "A Word of Cautious Dissent"

To the Editor: In a recent critique of the potential therapeutic value of cancer immunotherapy,[1] Dr. Hall sets forth a theoretical basis for limitations. He points out the weakness of human tumor antigens and relates that many human tumor antigens have proven to be products of normal cells which are either in the wrong anatomic location or of fetal origin. This last observation should theoretically lead to a kind of "horror autotoxicus" resulting from effective immunotherapy since tumor cells are not different from some ontogenic phase of their normal counterpart.

Yet extension of these objections provides a rationale which should make immunotherapy successful. Burnet's concept[2] is that the "immune system" resulted from an evolutionary pressure for "immune surveillance" of cancer. It would appear much more likely that "immunity" evolved as part of an ontogenic control mechanism necessary for the development of higher organisms. The "crudely compartmentalized" lower organism can differentiate with chemical gradients and inducing substances. In higher organisms, mesenchymal subcompartments interact with each other and with parenchyma in a physiologically and anatomically intricate way.

In these organisms, there would be evolutionary pressures for mechanisms which detect and repair the loss of integrity of compartmental interfaces during development and during repair of certain types of injury. Evidence for this viewpoint is the rapid removal of non-neoplastic ectopic parenchymal cells, the ontogenically late development of immunity in the "higher" organism, and the ability of organisms to detect antigens which are normally present some time during development.[3,4]

One may view invasive cancer as a breach in parenchyme-mesenchyme or mesenchymal subcompartment relationships. Going beyond a concept that many tumors are "no different from normal," I would propose that they are "less different from normal" than tumor and normal parent are from other tissues. This "less different" state should make tumors especially amenable to "immune controls," as a normal developmental control mechanism already exists for this very purpose.

This concept is in consonance with that of an antitumor effect of non-specific stimulation of "immunity." One simply has to "beef up" a normal developmental control mechanism. Those cancers which are due to true neo-antigens may not have much therapeutic edge on those which are "less different" from their parent tissue and hence recognizable by normal mechanisms.

The fact that clinical immunotherapy has not been a smashing success to date may be due to the limitation in capacity of a normal developmental mechanism which was not geared to handle a large volume of ectopic cells. With a better understanding of the normal monitoring of tissue compartmentalization under the direction of the "immune response," techniques to expand this developmental mechanism are very likely to be therapeutically exploitable with a large volume of ectopic tissue.

The current techniques for managing cancer include mutilation, deadly rays, and lethal poisons. These modern counterparts of trephining out evil spirits can only be thought of as temporizing measures. Diseases of fundamental biology must eventually be approached with fundamental biologic therapeutics. Learning to exploit the best nature has to offer is the best chance to make doctors more sophisticated than the diseases we treat, and will be essential for the much needed improvement in therapeutic ratios of cancer therapies.

Barry B. Lowitz, MD
Chief, Outpatient Section
Medical Service
Veterans Administration Hospital
Sepulveda, CA

REFERENCES

1. Hall TC: A word of cautious dissent. Seminars in Oncology 1:429-431, 1974
2. Burnet FM: The concept of immunological surveillance. Prog Exp Tumor Res 13:1-27, 1970
3. Baldwin RW, Embleton MJ: Neo-antigens on spontaneous and carcinogen induced rat tumors defined by in vitro lymphocytotoxicity assays. Int J Cancer 13:433-443, 1974
4. Girardi AJ, Repucci P, Dierlam P, et al: Prevention of simian virus 40 tumors by hamster fetal tissue: Influence of parity status of donor females on immunogenicity of fetal tissue and on immune cell cytotoxicity. Proc Natl Acad Sci USA 70: 183-186, 1973

The Diagnosis of Carcinoma and Benign Cysts of the Breast

To THE EDITOR: Dr. de Groot's paper, "Diagnosis of Carcinoma and Benign Cysts of the Breast—The Value of Needle Aspiration" [West J Med 122:99-103, Feb 1975] makes a valid case for a simple and useful procedure. However, no paper on diagnosis of carcinoma of the breast can ignore the most important contribution to the diagnosis of breast cancer in our medical generation. The use of x-ray examination of the breast, and perhaps more particularly the refinement of xeroradiography, has eliminated a good deal of the guess work which Dr. de Groot appears to accept in his paper.

He states: "If a carcinoma is so small that it escapes detection by the examining finger even when attention is directed to the specific area, a question that comes up is how one could have detected so small a lesion elsewhere in the same or the other breast, or at another time." These occult or nonpalpable cancers are the special province of mammography. Frankl[1] found 105 occult cancers out of 13,912 examinations. This represented about one-third of all cancers detected by xeroradiography. These occult cases were the more favorable ones by a vast margin. Occult cancers were associated with only 28 percent positive nodes as compared with dominant mass cases which were associated with 51 percent positive nodes. The number of negative biopsies for carcinoma (false positives) was 40 percent for radiologic studies as compared with 76 percent of biopsies based on physical findings. J. N. Wolfe[2] reported a similar incidence of occult carcinoma found on xeroradiographic examination. He found 30 percent occult carcinomas out of 462 cases of carcinoma. Thus the "question" of detecting the small or nonpalpable lesion has a very clear answer in the use of this valuable modality.

Dr. de Groot also suggests that in evaluating the borderline between lumpiness and discrete masses, the choice rests between repeated biopsies and bilateral mastectomy. This is an area in which mammography is of assured value. He also states that the modern sophisticated patient is used to having everything that is removed from her body sent to a pathologist. This same modern patient is aware of the value of mammography, and will probably request the procedure if her physician should fail to do so.

A tabulation of the clinical indications for mammography will encompass virtually all of the problem cases enumerated by Dr. de Groot. Such indications include fibrocystic disease and the diffusely lumpy breast, prior biopsy—especially with associated thickening, dominant mass—with particular reference to an unsuspected additional lesion in either breast, nipple discharge or breasts so large as to make physical examination unreliable. Among increased risk patients are those with prior mastectomy, family history of breast cancer, and the nulliparous or late parity patient. In summary, mammographic examination deserves a major role in diagnostic evaluation of the breast.

ROBERT B. ENGLE, MD
Laguna Beach, CA

REFERENCES

1. Frankl G: Xeroradiographic detection of occult carcinoma of the breast. Supplement to exhibit presented at the 60th annual congress of the American College of Surgeons, Miami, Oct 21, 1974
2. Wolfe JN: Analysis of 462 breast carcinomas. Am J Roent 121:846-853, Aug 1974

* * *

The Author Replies

IN THE EVALUATION of a patient who presents with a suspected cyst, mammography does play a role, as I did indicate in my paper. I am, therefore, somewhat surprised to hear Doctor Engle state that I "ignore" this modality. If I did not discuss mammography in detail, it was probably because the question was not whether clinical evaluation could replace mammography, but rather whether, when dealing with cysts, excisional biopsy can be replaced by noninvasive methods of diagnosis (of which mammography, next to palpation, is one) followed by needle aspiration.

There are, however, a number of practical questions which mammography cannot answer, in spite of the understandable but nonetheless only seemingly logical conclusion that, if mammography can detect occult cancers, it should be able to give even clearer answers about masses at a palpable stage. This is partly because of the nature of the problems involved, which mammography simply cannot be expected to solve, and partly because of the frequency with which these problems present themselves.

As an introduction, and because there is some overlap with questions which arise when dealing with cysts, I would like to point out that even the routine evaluation of "normal" breasts still mostly deals with palpable masses, in spite of the indeed amazing ability of mammography to discover malignancies which the human finger cannot even

begin to feel. This is partly due to the fact that the percentage of false positives and false negatives is at least 5 percent, but mainly because, for a number of practical reasons, mammography, at the present time at least, cannot serve as a mass screening method. Palpation, by the patient as well as the physician, thus is still our main line of defense, and is therefore an art which we should keep alive and cultivate as much as possible.

There is moreover the ever present problem of deciding what is merely an increase in density of a normal breast and what is a mass. Even completely normal tissue is occasionally by patients, and sometimes even by physicians, interpreted as a mass, usually when the lower, pendulous portion of a breast is examined with the thumb in front and the index and middle finger behind, whereby the mere thickness of the tissue grasped is the source of error.

The breast is unique in posing these dilemmas, and with such frequency, and because it is impractical and even not without hazard to perform mammography every time these problems arise, which is often several times in one year, they frequently have to be answered on the basis of clinical findings and judgment only.

When dealing with a suspected cyst, I agree that mammography, at least at the first presentation, is usually indicated, to confirm the diagnosis of fibrocystic disease, to closely evaluate the remainder of the breast tissue and, as far as the presenting mass is concerned, to confirm the clinical impression that the mass as a whole is a cyst and not one solid mass. The coexistence of a carcinoma with a cyst at the same time *and* in the same location would seem rather coincidental, and is in reality indeed extremely rare. The presence of a nonpalpable occult cancer, although of course not excluded, would seem even less likely.

There are, however, as mentioned above, a number of practical problems, which mammography cannot be expected to answer.

First of all there is after any aspiration the necessity of verifying that the mass has completely disappeared. If a mass does persist, a normal mammogram taken prior to aspiration obviously does not mean that the mass can be ignored.

Furthermore, when the area is rechecked after a few weeks, to see if reaccumulation of the cyst has taken place, it is clear that again only palpation can answer that question. Finally, if within several months another cyst, elsewhere in the breasts, presents itself, mammograms will generally not be taken again, and the question of a possible malignancy will therefore entirely have to be settled at the palpable level.

In summary, in spite of the truly valuable contributions of mammography to the detection of breast cancer, its findings always have to be supplemented with clinical observations; moreover, when dealing with cysts, and also during the routine evaluation of breasts, a number of practical questions arise which can be solved only by evaluating physical findings with the aid of expertise, experience and judgment.

These are faculties which are indeed not measurable and are rather subjective—which however does not make them synonymous with "guesswork."

WALTER P. H. DE GROOT, MD
Seattle

Surreptitious Knuckle Cracking

TO THE EDITOR: As a surreptitious knuckle cracker, I was intrigued by the article by Swezey and Swezey in the May issue of the JOURNAL (West J Med 122:377-379, May 1975).

It would seem, from the data obtained, that knuckle cracking may be a means of preventing degenerative arthritis of the metacarpal-phalangeal joints. Perhaps a study involving a larger group of subjects would help elucidate this point.

Conceivably, then, surreptitious knuckle cracking might be a healthful practice which would avoid "the chief morbid consequence of knuckle cracking" and should be generally encouraged.

PHILIP CHARNEY, MD
South Lake Tahoe

More on Laetrile

TO THE EDITOR: Despite well-meaning attempts to dissuade people from using Laetrile by using rational argument, nothing but failure can be expected from these efforts.

The use of coercive means to attempt to enforce these official points of view produces an unfortunate opposite effect. Cancer victims and their families almost universally respond by accusing organized government and organized medicine of conspiracy. The bumbling attempts to present a unified front contribute to this interpretation.

By making Laetrile into "forbidden fruit" this

policy of willful suppression expectedly produces motivation to circumvent these efforts and repeatedly confront representatives of these policies.

The enthusiasm for Laetrile would gradually waste away if it were permitted to be sold over-the-counter and the drug would end up gathering dust on back shelves.

Alas, with the encrustation of attitudes and official policies, I fear that attachment to these methods is too strong to permit a rational and effective tactic of de-regulation and benign ignoring of the drug.

However, for every action there is a reaction and since "it takes two to tango," no end to the controversy may be seen at this time.

TOD H. MIKURIYA, MD
Berkeley

Renal Imaging and Pyelonephritis

TO THE EDITOR: There has been considerable interest in the possibility of establishing an earlier diagnosis of acute pyelonephritis using nuclear imaging techniques. We have performed studies with renal cortical imaging agents (99m Tc-dimercaptosuccinic acid [DMSA] and 99m Tc-glucoheptonate [GHA]) as well as 67-gallium citrate as described in a recent article by Kessler et al (Kessler WO, Gittes RF, Hurwitz SR, et al: Gallium-67 scans in the diagnosis of pyelonephritis. West J Med 121:91-93, Aug 1974).

It has become apparent that renal localization of 67-gallium citrate occurs in a variety of disease entities as well as in some normal patients. Explanations for this are poorly documented but appear to be related to several factors, only one of which is acute suppurative disease. The *normal* excretory pattern for 67-gallium citrate includes a significant renal excretion in the first 12 hours; patients with altered serum iron binding capacity appear to have increased renal uptake of 67-gallium citrate[1] as do patients with a variety of neoplasms involving the kidneys.

Prompted by the Kessler article we reviewed 127 consecutive patients in our laboratory who had 67-gallium citrate scans for nongenitourinary tract problems. Seven patients (5 percent) showed well defined renal uptake of the material, one with unilateral localization. These patients' records were reviewed and one of the seven had symptoms or laboratory evidence of acute pyelonephritis.

Shortly after completing this review Frankel[2] reported renal uptake of 67-gallium citrate in 1.7 percent of 2,000 patients. In 13 autopsied cases 2 (15.5 percent) had normal kidneys, 9 (69 percent) had tumor involvement and only 2 (15.5 percent) had renal inflammatory disease.

Renal imaging with 67-gallium citrate, as well as with renal cortical agents (as suggested by Davies[3] with 197 Hg-chlormerodin), seems to be of value in the early diagnosis of acute pyelonephritis. It would appear, however, that we must proceed with caution in advocating studies that produce a significant number of "false positives." Exclusion of other causes for renal uptake of 67-gallium citrate is often difficult, and the possibility of performing further costly and more invasive procedures in normal patients should be borne in mind when interpreting this study. While Kessler and co-workers are to be congratulated for their application of this study to a difficult clinical problem, to conclude that the technique is "eminently useful in the diagnosis of acute pyelonephritis" seems a bit premature and possibly misleading in view of the frequency of renal uptake from other causes.

HIRSCH HANDMAKER, MD
Director, Nuclear Medicine Service
ROSE ANN ANDERSON, BS
Nuclear Medicine Technologist
Children's Hospital of San Francisco

REFERENCES

1. Hoffer PB, Bekerman C: Personal Communication
2. Frankel RS, Richman SG, Levinson SM, et al: Renal localization of 67-gallium citrate. Radiology 114:393-397, 1975
3. Davies ER, Roberts M, Roylance J, et al: The renal scintigram in pyelonephritis. Clin Radiol 23:370-376, 1972

Trauma Rounds

Chief Discussant
GEORGE F. SHELDON, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Sheldon GF: Transfusion practices in trauma patients (Trauma Rounds). West J Med 123:64-68, Jul 1975

Transfusion Practices in Trauma Patients

ROY CARLSON, MD:* The patient for discussion is a 33-year-old man, the victim of a stabbing. When admitted by ambulance to the emergency room, the patient had a 3 cm sucking wound to the right chest, appropriately covered by vaseline gauze. Blood pressure was unobtainable. Pulse was 120 beats per minute. On examination of the chest, it was noted that breath sound on the right was absent. The abdomen was distended and tender. The hematocrit was 43 percent; other screening laboratory values, including findings on urinalysis, were normal.

Resuscitation consisted of the placement of large bore catheters in all extremities, endotracheal intubation, insertion of a Foley catheter and insertion of a chest tube (right) which was productive of 600 ml of whole blood. As the patient did not respond to the rapid administration of crystalloid, other diagnostic studies were precluded and he was taken immediately to the operating room.

On exploratory laparotomy, a large laceration of both the medial and lateral segments of the right lobe of the liver was seen. During an extended right hepatic lobectomy, cardiac arrest occurred. Open cardiac massage was instituted while bleeding was controlled. After 15 minutes of cardiac massage, the heart was successfully defibrillated. Continued blood loss from the liver as well as from cutdown sites occurred.

During the four hour operation, blood product replacement was 50 units of whole blood, 11,000 ml of plasma, and 20 units of platelet packs.

Following operation, the hematocrit was 22 percent. In the recovery room 4,500 ml of fresh warm type-specific blood was administered with ten additional platelet packs. During the subsequent two days, high output renal failure, hepatic failure and progressive pulmonary insufficiency developed.

During 14 days in hospital, the patient was given a total of 105 units of whole blood (27 fresh), 32 units of fresh frozen plasma, 64 units of platelet rich concentrates and 120 platelet packs—for a total of 320 units of blood products. The subsequent course was progressive recovery from respiratory and renal insufficiency. The patient returned home after six weeks in hospital with minimal postinjury residual.

F. WILLIAM BLAISDELL, MD:† *What was the difficulty in controlling the bleeding from the liver, Dr. Carlson?*

DR. CARLSON: There was a transverse injury to the liver in which both segments of the right lobe

*Chief Resident, Trauma Service, San Francisco General Hospital.

Sponsored by Northern California Trauma Committee, the American College of Surgeons. Supported in part by U.S. Army Contract No. DADA17-72-C2030 and NIH Grant GM18470.

Reprint requests to: D. D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco, CA 94110.

†Chief of Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco.

and the medial segment of the left lobe were involved. All raw liver surfaces and the hepatic veins were bleeding. Because of profound shock and extensive soft tissue injuries, it is probable that disseminated intravascular coagulation syndrome developed. The bleeding was presumably aggravated by an inability to produce coagulation factors due to liver malfunction. Because the patient's entire blood volume was replaced several times over, the problem may have been aggravated by some transfusion deficit as well.

DONALD D. TRUNKEY, MD:* *Our discussant today is Dr. George F. Sheldon, Chief of the Trauma Service, San Francisco General Hospital, whose research interests are in red cell physiology. Dr. Sheldon, would you comment on this patient's transfusion therapy?*

GEORGE F. SHELDON, MD:† Considerable interest is being focused on blood use and resources. In June 1972 the National Research Council reviewed techniques and deployment of red blood cell preservation.[1] A similar conference was held by the American National Red Cross in May 1973. In *The New England Journal of Medicine,* July 1974, the current status of red blood cell preservation was reviewed as it applies to an evolving National Blood Policy.[2]

Blood stored in any preservative is an altered product. With storage, erythrocyte, clotting and platelet function deteriorate and metabolic by-products increase. Food and Drug Administration regulations limit storage of blood to 21 days. This 21-day preservation is based on the requirement that 70 percent or more of the administered red blood cells survive more than 24 hours.

After it was shown in 1967 by Chanutin and Curnish and by Benesch and Benesch that a red blood cell's ability to unload and load oxygen was dependent on intracellular organic phosphates—primarily 2,3 diphosphoglycerate (DPG) and adenosine triphosphate (ATP)—emphasis has shifted from red cell survival to red cell function.[3,4] Intracellular organic phosphates, primarily DPG and ATP, are by-products of the glycolytic cycle of the red cell. During the first week of storage in Acid Citrate Dextrose (ACD) the deterioration is 50 percent of the initial DPG values. Within 14 days of storage in citrate phosphate dextrose (CPD), 50 percent of a stored cell's organic phosphate will be gone. Although acid citrate dextrose, the preservative developed during World War II, is effective, most blood banks have changed to citrate prosphate dextrose during the past year. This in part is due to better preservation of red cells in CPD.[5]

Recent research may alter blood preservation and transfusion practices. Red blood cells stored by conventional methods can be rejuvenated at almost any period of time by incubation with purine nucleotides and inorganic phosphate and dextrose. It is possible to wash and freeze red blood cells and administer them at remote periods from the time of donation. The addition of many substances, such as corticosteroids, ascorbic acid and dihydroxyacetone, will maintain red cell organic phosphates and oxygen transport for periods of time considerably longer than that possible by current methods.

Although methods for preserving red cells longer than 21 days are available, Food and Drug Administration approval for increasing the storage time has not occurred for many reasons. Proof is unavailable that red cells high in 2,3 DPG have clear-cut advantages over blood stored by conventional methods. The considerable increase in expense created by rejuvenation and freezing techniques has precluded universal application. Blood is a human resource; availability of healthy donors determines the need for prolonged preservation practices to some extent.

Our laboratory has addressed itself to the question of *in vivo* rejuvenation of red cells during the past two years. The patient who receives large volumes of blood stored over one week has blood circulating which tenaciously holds onto oxygen and may release it to the tissues less readily. The reasons for enhanced affinity of hemoglobin for oxygen are multiple. Stored blood, with its loss of diphosphoglycerate, has an increased affinity of hemoglobin for oxygen.

Blood preserved at 4°C (39.2°F) to prevent bacterial growth will result in the patient being cooled during its administration. If the patient shivers, oxygen consumption needs are increased. Hypothermia causes an increase in hemoglobin oxygen affinity in addition to DPG deficiency. When a critical emergency requiring transfusion exists, it is reasonable blood bank policy to use blood closest to the end of shelf life. Blood nearing expiration will have low DPG levels. Of the 116 patients who received the equivalent of an exchange

*Assistant Professor of Surgery, University of California, San Francisco; Chief of Surgery, Mission Emergency Hospital.

†Assistant Professor of Surgery, Chief of Trauma Service, and Associate Director, Trauma Center, University of California, San Francisco.

transfusion (10 or more units of blood) during the past year in our unit, the mean shelf life was 11 days.

Another factor which increases the affinity of hemoglobin for oxygen is metabolism of the citrate preservative. Although intrinsically acid in liquid storage, metabolism of the citrate moiety by the liver results in metabolic alkalosis. Metabolic alkalosis increases the affinity of hemoglobin for oxygen.

Many physiologic mechanisms in the injured patient increase hemoglobin oxygen affinity in addition to those related to blood transfusion. Hemorrhage is a stimulus to hyperventilation with resultant respiratory alkalosis. The kidneys conserve sodium following shock with conservation of bicarbonate. *In summary, 2,3 DPG diminution, citrate metabolism, hypothermia, and metabolic and respiratory alkalosis all greatly increase the affinity of hemoglobin for oxygen in the transfused, resuscitated patient* (Figure 1).

Compensation for increased hemoglobin-oxygen affinity can be obtained initially by an increase in cardiac output. Sufficient cardiovascular reserve to compensate for temporary red cell dysfunction, is usually present. In a younger patient, cardiac output will increase by as much as two to three times normal. In an older patient with limited myocardial reserve, or in a patient with a heart injury, compensation for this defect may not be possible and a deficit in oxygen available to the tissue of the body will result. Defective red cell phosphate levels and any alkalosis generated during resuscitation, stimulates the enzyme phosphofructokinase and diphosphoglycerate is rapidly manufactured. In our study of patients who have received massive transfusions, the defect in organic phosphate levels usually is reversed by 24 hours.

Although the red cell mechanisms for the recovery of oxygen transport is regenerated in a day or so, the metabolic toll in a severely injured patient is unknown. In a number of instances we have noted that lactic acidosis, indicating a persistent oxygen deficit, did not improve until red cell function returned to normal (Figure 2).

In the patient discussed today, transfusion needs were so massive that the older blood in the bank was rapidly depleted and fresh blood was administered early. As a result, our studies of red cells in this patient showed only a minimal early increase in hemoglobin oxygen affinity.[6] As a matter of fact, I would go so far as to suggest that the patient's survival from this critical injury may have resulted from prompt correction of the red

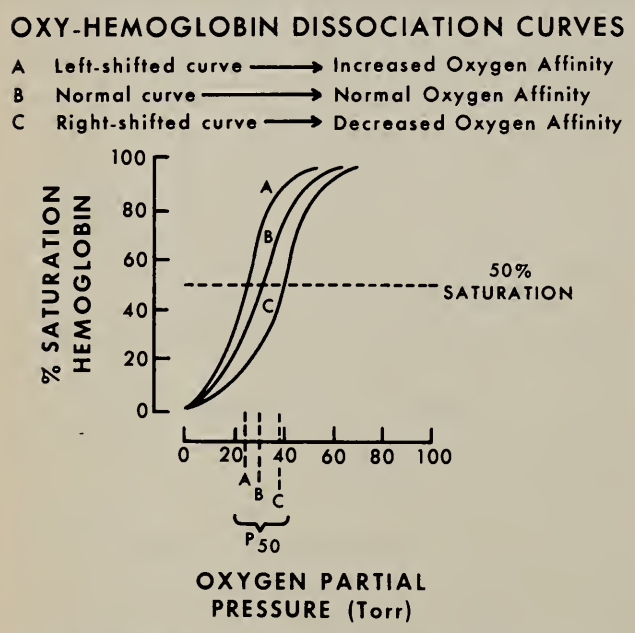


Figure 1.—The oxy-hemoglobin dissociation curve provides a measure of the red blood cell's role in oxygen transport. The $P_{50\,\text{mm of Mercury}}$ (oxygen tension) describes the point at which hemoglobin is half-saturated. Low disphosphoglycerate (DPG) values, hypothermia, hyperventilation and postresuscitation metabolic alkalosis contribute to high affinity hemoglobin (A) and compensation is by increased cardiac output and venous oxygen extraction.

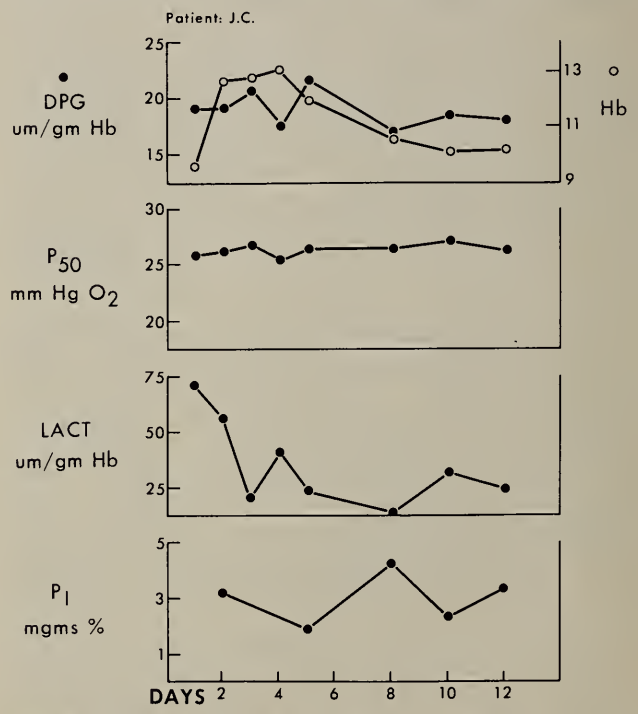


Figure 2.—Transfusion and metabolic measurements in the patient presented. Following resuscitation, P_{50} and disphosphoglycerate (DPG) levels were transiently low. Endogenous rebuilding of DPG plus fresh blood resulted in satisfactory compensation and clearing of lactic acidosis.

cell defect since the margin for survival was very thin.

A PHYSICIAN: *Dr. Sheldon, what is the transfusion lesion?*

DR. SHELDON: The massive transfusion defect is one of deterioration of red cell, platelet and clotting factors. We have found that significant deterioration in these multiple measurements of blood function occurs almost uniformly with a 10 unit transfusion in an adult. We arbitrarily define "massive transfusion" as that equivalent to the blood volume of the patient. The red cell defect has been discussed in some detail. Additional discussion of clotting and platelet needs will be a subject of a subsequent seminar. In brief, the coagulation measurements hold up well with only Factors V and VIII (labile factors) deteriorating significantly during storage. Since the body's capability for regenerating clotting factors is great, coagulation problems rarely develop secondary to massive transfusion alone.

Massive transfusion, however, coupled with shock and devitalized tissue, may produce intravascular coagulation and result in depletion of clotting factors faster than they can be manufactured or replaced. Fresh frozen plasma is the specific treatment for these coagulation defects. More often than coagulation defects, however, we see defects in platelet function. Normally, refrigerated blood contains platelets which, when transfused, do not function immediately. In circumstances of massive transfusion, a platelet defect can be assumed. This defect is a common cause of oozing or of abnormal blood loss. Platelet transfusion is specific treatment for this lesion.

DR. BLAISDELL: *Dr. Sheldon, what is the optimal type of transfusion to use if and when anemia develops later in the postinjury period?*

DR. SHELDON: After recovery from massive transfusion, the patient is often anemic. If the problem is anemia without hypovolemia, then a transfusion of packed red blood cells is the unit of choice. Packed red blood cells are prepared from whole blood by centrifugation and separation of plasma fractions. The shelf life of packed red blood cells is 21 days, the same as that of whole blood. Removal of platelets and leukocytes may diminish the sensitization of some patients to transfusion units and is an additional reason for the use of packed cells as standard practice. Anemic patients should be approached from a functional point of view and not from the standpoint of a pure drop in hematocrit. A young patient can tolerate anemia of 7 to 8 grams per 100 ml of hemoglobin without symptoms. Red cell organic phosphate increases in anemia, restoring increased oxygen transport capability toward normal and this compensation requires only a day or so. However, any patient whose loss of blood volume is acute should not be challenged further and should receive whole blood.

DR. TRUNKEY: *Dr. Sheldon, would you comment on citrate intoxication?*

DR. SHELDON: Citrate intoxication remains a vague complication of blood transfusion. In a hypothermic patient, citrate will be metabolized slowly and excessive blood citrate levels theoretically could produce decreases in blood ionized calcium levels. It is unclear whether this is a significant problem clinically since our ability to measure ionized calcium has been limited. With more frequent use of rapid massive transfusion we have seen more problems of myocardial malfunction which seems to respond to calcium infusion. Particularly when potassium levels are high, abnormalities of myocardial electrical conduction may occur. Although this issue is unsettled, a reasonable approach is to administer calcium chloride, 2 ampules slowly for every 2 units of blood, during the massive transfusion event. With the availability of new electrodes for measuring ionized calcium, a more rational approach to this form of therapy should occur.

A PHYSICIAN: *How do you manage hypothermia in patients such as the one presented today?*

DR. SHELDON: Hypothermia is one of the most significant acute problems of massively transfused patients. Our practice is to warm the blood in water bath warmers. Microwave blood warmers are currently not in use because of their tendency to heat unevenly and destroy cells.[7] We also warm the patient on the operating table by irrigating any accessible body cavity with warm saline solution.

A PHYSICIAN: *Dr. Sheldon, what is fresh blood?*

DR. SHELDON: The definition of fresh blood is arbitrary. Fresh blood, in terms of red cell function, could be defined as blood stored less than one week. It should be emphasized again that blood stored 21 days is acceptable, as far as we know, unless transfusion is extensive enough to produce what amounts to an exchange transfusion.

The massively transfused patient may on occasion need replacement of all blood components for clotting, platelet and red cell function. Under these circumstances one has the choice of simultaneously administering all three components separately or using fresh unrefrigerated warm blood taken directly from the donor and given to the patient. By so doing, the patient receives red cells with normal function, dilutional thrombocytopenia is corrected and all clotting factors will be replaced.

In 1972, with the Irwin Memorial Blood Bank of the San Francisco Medical Society and the cooperation of the San Francisco Police Department, a fresh warm blood program was established at San Francisco General Hospital. This program was begun to ensure availability of blood products for the unusual patient whose transfusion needs were excessive and massive. This has the advantage of simultaneously correcting all potential deficits. In most instances, however, citrate phosphate dextrose preserved blood less than one week old combined with six to eight platelet packs is sufficient and adequate for correction of most massive transfusion deficits in which intravascular coagulation is not a problem.

Component therapy is the standard recommended practice of our hospital and is optimal treatment for almost all routine problems. The use of whole blood to meet transfusion needs is inappropriate, unnecessary and wasteful of a major resource. In most instances, a blood transfusion unit is given for a single component—red blood cells, platelets or clotting factors—depending on the need of the specific patient involved.

REFERENCES

1. Chaplin H Jr (Ed): Preservation of Red Cells. Washington, DC, National Academy of Science, 1973

2. Chaplin H Jr, Beutler E, Collins JA, et al: Current status of red cell preservation and availability in relation to the developing national blood policy. N Engl J Med 291:68-74, 1974

3. Chanutin A, Curnish RR: Effect of organic and inorganic phosphates on the oxygen equilibrium of human erythrocytes. Arch Biochem Biophys 121:96, 1967

4. Benesch R, Benesch RE: The effect of organic phosphates from human erythrocytes on the allostearic properties of hemoglobin. Biochem Biophys Res Comm 26:162, 1967

5. Bunn HF, May MH, et al: Hemogloblin function in stored blood. J Clin Invest 48:311-321, 1969

6. Sheldon GF, Lim RC, Blaisdell FW: The use of fresh blood in the treatment of critically injured patients. Accepted for publication, J Trauma, 1974

7. Miller RD: Complications of massive blood transfusions. Anesthesiology 39:82-93, 1973

Refer to: Guidotti TL: Medicine, critical science and the real world (From a Medical Student). West J Med 123: 69-70, Jul 1975

Medicine, Critical Science and the Real World

TEE L. GUIDOTTI, MD, *Baltimore*

A MAN WOULD HAVE to be a fool to buy a map with just one road printed on it. Assuming that it led to his intended destination in the first place, it may not be the best way to go, he may bypass many places where he might wish to stop, and he has no way of correcting himself should he become lost.

This is precisely what happens when "basic" research is sacrificed for "applied" research, or when an attempt is made to impose a schedule on discovery and application.[1,2] Science depends too heavily on serendipity and the astute observation and flash of insight.[3,4] The concept that science can be programmed is derived from industrial "R&D" (research and development), which with a few outstanding exceptions is heavy on the "D" and light on the "R". Basic science is by definition investigation into areas with no immediately foreseeable application.

This is the mode of science which fills in the uncharted white spaces of our metaphorical map, the mode on which we fall back when confronted with the unexpected and from which come so many fortuitous observations and unanticipated applications, and an understanding of mechanisms. In short, it is basic science that pieces together a world picture. Without some comprehension of the totality, some perspective within which to place each new thrust of applied and directed science, we are doomed to constant repetition of the past excesses of technology: smog and the automobile, microbial resistance and antibiotics, sarcomas and radium watch dials, soil and water degradation and strip mining, phocomelia and thalidomide.

Obviously basic science does not have a ready answer for every question as it arises, but clearly such answers are much closer when workers have been allowed to extend their investigations into areas that appeared improbable of application before the question arose. One example, drawn from outside medicine and chosen for its lack of glamour, is the large body of work on food chains and energy budgets in terrestial and aquatic ecosystems. How many graduate students and junior faculty spent months wading in muddy marshes or sweltering in abandoned cornfields to watch squirrels eating seeds and grebes catching fish may never be known. The concepts that developed from such tedious and esoteric work, however, have proven enormously useful in our understanding of the biosphere, and have proven essential in the development of ocean resources, agriculture and theoretical biology. They are now finding their way into urban planning. A striking example closer to home for most of us was the basic research in immunology and virology which led to the development of a poliomyelitis vaccine.

Basic science and applied science are the two commonly accepted modes of research, the latter being associated with technology. For hundreds of years, until the emerging European middle class discovered the enormous profit to be realized by combining their hobby of science with their business of industrialization, science and technology scarcely spoke to one another and followed entirely separate historical paths. Lavoisier, Watt and Pasteur showed that directed scientific research in the service of technology could prove immensely productive, and so developed the mode

The author was a fourth-year medical student, Class of 1975, University of California, San Diego, School of Medicine, when this article was written. He is now an intern in the Department of Medicine, The Johns Hopkins Hospital, Baltimore.
Submitted April 28, 1975.
Reprint requests to: T. L. Guidotti, MD, 534-A North Bond St., Baltimore, MD 21205.

of applied science. Unfortunately, the same law of data processing governs applied science: garbage in/garbage out. The quality of the work is independent of the worthiness of the goal and the quality of the assumptions and data. We are treated to the spectacle of millions of dollars spent to develop redundant drugs to circumvent patents while other areas of biomedical science are starved for funds.

In the broad perspective of the history of science, the emergence of a new mode* of science is an exceedingly uncommon event. It is very exciting that this appears to be happening in our time. The new mode is named "critical science" by its principal analyst, Dr. Jerry Ravetz, of the University of Leeds (England), who describes it as a new approach which critically evaluates and analyzes the impact of technological developments within the context of the real world (not the engineer's world of simplifying assumptions), and which draws primarily on basic science and collaborative critical research to predict, document and correct physical and human problems of technological origin.[5]

Credit for the first sustained organized effort in critical science goes to Dr. Barry Commoner, of Washington University in St. Louis, whose work dates to the rise in public concern over radioactive fallout in the 1950's.[6] He has worked since then through the American Association for the Advancement of Science, the Scientist's Institute for Public Information, the St. Louis Committee for Environmental Information and his Center for the Biology of Natural Systems. His work has focused mostly on environmental problems and he has assembled a young and bright community of researchers around him.[7]

The one essential tool of critical science is knowledge, in the sense of both data and unifying concepts. To this end it requires the highest quality of original research and thoroughgoing comprehension of many scientific disciplines. It stands to become a powerful integrative force in the scientific world, a confluence of specialities without amalgamation into a bland and superficial generalism.

In our own province of medicine, which transects so many other disciplines, such a mode of science is also evident, perhaps most clearly demonstrated in the little-heralded emergence of a newly coherent field of study which treats ecological factors in human settlements pertinent to health. This has been variously called ecological medicine, medical ecology, human ecology, environmental medicine and—the term that I prefer because it allows for precise definition with a minimum of false connotations—environic medicine.[8,9]

This is an inauspicious time to found a new discipline. René Dubos pointed out that "the requirements of human ecology for new kinds of research facilities and for a change in intellectual opinion will provide a ready excuse for neglect . . . this science will develop only if society recognizes that ecological knowledge is essential to its welfare . . . "[10] Not the least of many dangers that this new discipline faces is the bandwagon effect that has plagued the ecology movement since its early rise in public attention and which is also evident today in cancer research. On the other hand, encouraging signs include the prospect of healthy support for basic and critical research in the effects of hazardous substances. The National Institute of Environmental Health Sciences, for example, is supporting a series of Environmental Science Centers at academic centers.

We can only wish that this bold new discipline will fulfill its promise as a valuable study in its own right and as a model for critical science in medicine. Bertrand Russell in 1924 well characterized the impact of a scientific discipline: "A science may affect human life in two different ways . . . without altering men's passions or their general outlook, it may increase their power of gratifying their desires. On the other hand, it may operate through an effect upon the imaginative conception of the world, the theology or philosophy which is accepted in practice by energetic men."

*A mode is a fundamentally different approach to acquiring or applying knowledge, as opposed to a discipline, a practice or a topic.

REFERENCES

1. Baram M: Social control of science and technology. Science 173:535-539, May 7, 1974

2. Thomas L: The planning of science. N Engl J Med 289:89-90, Jul 12, 1973

3. Stent GS: Prematurity and uniqueness in scientific discovery. Sci Am 227:84-93, Dec 1972

4. Wilson RR: My fight against team research. Daedalus 99: 1076-1087, Fall 1970

5. Ravetz J: Towards critical science. New Scientist 51:681-683, Sep 23, 1971

6. Commoner B: Science and Survival. New York, Viking Press, 1966

7. Guidotti TL: Of Commoner and the commons. Alternatives (Trent Univ, Ontario, Canada) 2:32-33, Autumn 1972

8. Guidotti TL: Environic medicine—Steps in the foundation of the discipline. The Pharos of Alpha Omega Alpha 37:17-23, Jan 1974

9. Sachs DP: Towards a comprehensive program of ecological medicine. The Pharos of Alpha Omega Alpha 34:147-150, Oct 1971

10. Dubos R: The crisis of man in his environment, *In* Proceedings of the Symposium on Human Ecology. Washington, DC, U.S. Public Health Service Publication No. 1929, 1968

Refer to: Wiseman LW: Res ipsa loquitur (Professional Liability). West J Med 123:71-75, Jul 1975

Res Ipsa Loquitur

L. WARD WISEMAN, MD, *Anaheim*

EDITOR'S NOTE: *The thoughts expressed in this article seem of unusual interest and also timely. They are presented for discussion and in the hope they may contribute something to the resolution of this now critical national problem.*

—MSMW

EVENTS OF THE past six months indicate that present methods of handling medical malpractice suits are ineffective. To anyone familiar with the tort system, the obvious inability of the "judicial approach" to cope with the problem of medical malpractice is a source of satisfaction. In this context the numerous well-meaning proposals advanced by concerned persons to modify the system should be viewed with concern rather than approval. The greatest possible tragedy resulting from this crisis would be to reform the tort system rather than to replace it.

The judicial solution for medical malpractice disputes is an archaic social tool. It evolved from legal principles which had merit in earlier centuries for the simple societies and primitive medicine of those times. Doctors who operate while drunk and produce injury as a consequence are guilty of malpractice in a basic moralistic crime-and-punishment sense. This is a fundamental situation of right and wrong, black and white involving a simple ethical question upon which all good men can agree regardless of education or experience. The legal system is designed for this type of problem. It was inevitable that it would be adapted to handle early medical malpractice disputes, particularly since society had not yet developed alternate ways to help injured patients.

Submitted May 14, 1975.

Reprint requests to: L. W. Wiseman, MD, 1264 Dwyer Drive, Anaheim, CA 92801.

Problems arose when society became more complex and medicine became more technical and successful. Medical catastrophes less often killed but, rather, crippled people; the courts were faced with more and more disabled victims of medical accidents unable to provide their own support. Public morality no longer permitted them to be ignored. The increasing sophistication of medicine produced changes in value judgments and professional reasoning which were difficult to comprehend without medical experience so that medical and legal definitions of malpractice began to diverge. Law by reason of its existence must make choices and issue judgments—and judgments are absolutes. A verdict is a win-or-lose, all-or-nothing result. Law further requires an adversary system, a plaintiff and a defendant, to activate the legal machinery to produce what is ultimately an arbitrary decision. Basic contradictions developed because increasing numbers of medical malpractice actions were not black and white but shades of gray.

The legal code as it stood could not cope with these new varieties of medical suits without changing its basic precepts, and it could not change its basic precepts for medicine without jeopardizing its credibility for other types of disputes. In an attempt to resolve this dilemma, the courts began a series of ethical compromises and legal camouflages which ultimately led to the moral and logical dry rot of the tort system today. Since most

malpractice suits no longer fit the legal machinery, the legal definition of malpractice was altered so that they would; res ipsa loquitur, statute of limitation, informed consent, and the like appeared in accelerating succession. Since the injured patient could not sue "fate" it was necessary to make the doctor a surrogate defendant so that the legal system could operate. The very features that made the tort system effective in other fields made it incompetent to handle medical malpractice actions with justice and honesty.

Every man in the course of living absorbs rudiments of law, finance, engineering, and so forth. He can adapt into a proficient jurist quickly in those fields which are a part of his everyday life. He is uniquely isolated from medicine and so the mandates of the operating room are completely foreign to his past experiences. How then can a judge or jurist be educated to a professional competence sufficient to decide medical malpractice during a brief trial when it takes the physician years of education and experience to gain the necessary expertise? The point is that medicine is different. In most occupations, man's will and intellect have almost complete control over the outcome; human negligence is usually a direct cause of untoward results in other professions. In medicine, to a much more significant extent, God controls the outcome. A person who contends that malpractice is the cause of even a majority of malpractice suits is simply ignorant about the subject. The physician is often as much the victim of the accident that caused the medical catastrophe as the patient himself. Why should a doctor be liable for what he did not cause and cannot prevent? Law places no other profession in this type of jeopardy. The doctor as a physician deserves special treatment because his professional substrate is different. The doctor as a man demands only the same treatment as other citizens.

It is undeniable that one working system should not be discarded before another is available to replace it. One alternate to the tort system would be the creation of a single, statewide *Medical Catastrophe Insurance Corporation* governed by a commission composed of representatives of law, medicine and the public. The corporation would be funded by annual premiums paid jointly by every licensed hospital and hospital medical staff. In addition, on admission to a hospital each patient would personally pay a separately itemized fee to the insurance corporation. This fee would be on a sliding scale based on monthly income. The purpose of the insurance corporation would be the provision of financial aid to persons injured in medical accidents. The corporation would set premiums for each hospital and hospital medical staff (considered as a unit) and for patients in hospitals at actuarially determined levels sufficient to cover its expenses. The corporation would also have the exclusive right to initiate law suits against a hospital-hospital staff unit; the issue of such suits could not be malpractice itself but only whether the hospital and its medical staff governed itself in such a way as to protect the public against malpractice. A judgment against the hospital-hospital staff unit would not only require upgrading of medical monitoring procedures to accepted standards, but would also result in the assessment of additional punitive premiums from the hospital and staff in an amount and of a duration set by the court.

Doctors would be required by law to join at least one hospital staff. As staff members they would pay their proportionate share of hospital-hospital staff unit expenses under this plan (annual insurance premiums, joint legal fees, punitive fees, and the like). They would be required to contribute their share of service time for medical staff activities. The hospital-hospital staff unit would be legally responsible for inpatient and outpatient professional activities of member physicians, hospital administration and hospital auxiliaries. In return, the medical staff could have the exclusive right to conduct malpractice proceedings against individual staff physicians. These proceedings would be carried out within the medical staff committee system in accordance with the staff constitution—the form of which would be prescribed by legislation. The finding of malpractice and the corrective action recommended would have the effect of law.

Patients injured in medical accidents would receive automatic assistance upon application to and certification by a *Medical Accident Review Committee*. Application for assistance could be made by the patient, the family, the attending physician, the hospital administration or the social service nurse acting as an ombudsman. The scope of the medical accident review committee could be countywide or local depending upon volume. It would be composed of physicians, hospital ad-

ministrators, welfare workers, consumer advocates or representatives of any other interested group. Its only function would be verification of the occurrence of a medical accident and certification of termination of disability or completion of rehabilitation. Upon confirmation of the accident, the insurance corporation would automatically dispatch monthly payments to the injured patient based on the cost of maintenance if the patient is unemployed or a minor, on the cost of housekeeping and child care expenses if the patient is a housewife, or on a percentage of the current earning power if the patient is the head of a household. A deductible waiting period of one month would be utilized to discourage nuisance claims. Payments would be supplemental to coexisting benefits from industrial or state disability programs or from private insurance. Rehabilitation and reeducation would be covered if appropriate; additional medical costs would be covered until the advent of national health insurance. Aid would be stopped upon medical recovery, upon completion of rehabilitation or retraining, or upon death. Disability persisting beyond two years and interfering with employment would be considered permanent and total, and would constitute the basis of transfer of further care to the Social Security program. A final lump sum payment consisting of the unpaid balance of the patient's lost earnings not covered by the monthly maintenance payments would be made a stated period of time after return to full employment.

The outstanding characteristic of this system is its frankness and honesty. Public participation in the cost of medical catastrophe protection would predicate acceptance that accidents are an inherent part of medical treatment, risks to which everyone is eventually exposed, and therefore the responsibility of everyone. The public has always paid the premium for malpractice but a patient's contribution would no longer be hidden within a doctor's bill.

Another feature is that it asserts the principle that victims of medical accidents are entitled to public help as a right not subject to litigation. No longer would an injured patient be forced to sue his doctor in order to survive. A physician no longer would be compelled to act as a substitute for society in order to be the defendant necessary for the adversary system to function. A patient who is slightly injured would receive the aid he deserves, just as would a badly injured patient; no longer would an injury need to be bad enough to arouse the financial interest of a lawyer in order for the injured patient to be helped. Aid would be given early when the need is greatest and not after years of depositions, conflicting medical examinations and traumatic court appearances. The payments would be made directly to the patient and in accordance with his monthly needs.

For the first time the public would be really protected from malpractice. The hospital medical staff committee system, under the plan, is given the exclusive power to determine the fact of malpractice and to punish for it, correct it and prevent it. The penalty for a negligent doctor no longer would be an ineffective and temporary rise in malpractice premiums but mandatory reeducation, permanent loss of privileges or loss of license. A bad doctor would never be freed to continue to harm the unsuspecting public. Personal liability for fault, under this approach, is direct, just and effective rather than spurious and illusionary. On the other hand, the doctor would know he would be judged objectively by professional peers on medical facts rather than legal mumbo jumbo. Defensive medicine not only would not be needed but would be a cause for censure. The fact that a doctor is otherwise immune from malpractice litigation would filter out the fear and distrust that now poison the doctor-patient relationship.

In this proposal, only the insurance corporation could initiate law suits in the old tort sense of the word. These suits would be directed only against the hospital and hospital staff, not based on the fact of malpractice but on the failure of the hospital-hospital staff unit to adequately protect against malpractice. This provision recognizes the increasingly obvious fact that while the courts are incompetent to judge on the occurrence of malpractice they are competent to determine whether adequate measures to protect against malpractice have been taken. This provision also would place the hospital administration and the medical staff in the same lifeboat and provide the incentive for each to watch and help the other.

These suggestions involve the grant of no special privilege to medicine. There have always been unique subgroups within a national community to whom society has granted limited legal autonomy. Canon law, for example, has been accepted for centuries. The idea of professionals

judging and sentencing professionals is a carry-over from the California State Bar where lawyers are investigated and punished by fellow lawyers (that is, the State Bar and California Supreme Court). The grant of immunity to doctors from individual malpractice suits is a restatement of a principle established in industrial law where an employer cannot be sued twice for fault, both as an employer and as an individual. The physician should not be placed in double jeopardy through liability for suits both as an individual person and as a medical staff member. The requirement that hospitals and staffs exert quality control in health care delivery is in keeping with recent trends in consumer law where a producer is responsible for protection of the public where the public lacks the technical expertise to protect itself.

A legitimate concern is whether a modified no fault plan such as this would prove more economic than the present system. The problem of determining justifiable periods of disability after an accident is difficult; the availability of automatic compensation for medical accidents appears an open invitation for malingering. Procedures, data and computer techniques already developed by hospital utilization committees and Professional Standards Review Organizations (PSRO's) to monitor the duration of hospital stays would appear readily adaptable to the creation of standard periods of disability. Patient awareness of these standards would provide psychological coercion for recovery. Public financial participation in the program and public membership in the medical accident review committees would produce an element of peer compulsion for cure. Aid would be given promptly and automatically before compensation neurosis can develop. The initial waiting period, in addition to the fact that compensation would be based on a percentage of lost earning power, would add a financial prod for prompt convalescence. The fact that this plan would only supplement other sources of maintenance and that its duration of action would be limited to two years—following which, responsibility for care would be transferred to the Social Security program—would effectively limit exposure and encourage recovery. The final lump sum payment after successful return to work provides the carrot for full independence. Nobody gets rich under this plan.

In the final analysis malingering is an inevitable part of any plan that attempts to help people. It cannot be said that this system completely represses it. People malinger in medicine because being sick is preferable to their normal life; the ability to make everybody happy is beyond the scope of this proposal. The tort system does not prevent malingering either; it merely limits the reward for malingering to a few badly injured patients. Political mechanisms are self-fulfilling and any system that assumes people will cheat forces them to cheat. This proposal treats patients fairly and it does not require an excess of idealism to assume that the public will treat it fairly in return.

In addition, the intangible economic advantages of this plan are enormous. It would utilize organizations already functioning and doing for free exactly what they would be required to do under this proposal. The medical staff-hospital board of director system is time tested and efficient, requiring only the incentive of legal authority to become operative as outlined here. Hospital social service nurses could easily adapt to becoming ombudsmen. Medical and paramedical professional societies and consumer organizations already in existence would be fruitful sources of interested and experienced volunteers for the medical accident screening committees. The absence of "defensive medicine" would decrease medical costs. The private lawyer-insurance company complex no longer would siphon off 70 to 80 percent of each compensation dollar. The simple certification procedure would conserve valuable lay and professional manpower hours. The restriction of formal tort procedures to the master insurance company and the hospital-hospital staff units would conserve court room space and ease judicial calendars.

A final asset of this plan is that it looks to the future rather than to the past. The care of the injured patient, under the proposal, is recognized as a welfare rather than a legal problem allowing intermeshing with and substitution by other existing or contemplated social action programs with gains in service and economy. It might be argued that this simply takes the money out of the public's left pocket instead of its right but at least the cost of care is widely distributed instead of being exclusively levied against the sick and injured who are the very ones least able to afford it. This scheme is realistic in its cognizance that ours is no longer an opulent society. While it acknowledges an obligation to help the victims of medical

accidents it recognizes that this aid can no longer be unlimited. The era of cheap oil, big cars and repeated economic surpluses is almost over. Patient aid would be given for a limited time and be based on lost earning power only. Society can no longer afford the luxury of lifetime compensation for pain and suffering, loss of cohabitation and other risks of life.

Basic changes in the form of health care delivery are beginning which this plan recognizes and complements. Medical accountability is a requirement of all proposed national health programs. The growing economic marriage between hospitals and doctors and their joint involvement in total medical care is recognized and encouraged under the plan. The increasing percentage of salaried doctors, the economic nutcracker of fixed medical fee schedules and rising overhead and the emergence of Health Maintenance Organization (HMO) types of mass medical care contracts are perceived as indications that medicine will not much longer be a high profit industry, and be able to pay for this problem by itself. It seems doubtful that government, with its growing presence in medicine, will be as tolerant of the gross inefficiencies and exploitations of the tort system as organized medicine has been. Medical care is rapidly becoming a team effort involving the coordinated activities of a number of equally responsible physicians and auxiliary professionals; this development is accepted by making the hospital-medical staff complex, rather than the individual physician, responsible for the prevention of medical catastrophes.

The assertion that society must accept the tort system as the only available solution for the problem of medical malpractice is obviously not valid. It is the last desperate argument of legal chauvinism. Social engineering has advanced to a point where the public is no longer restricted to the crude choices of frontier days. The tort system in medicine was designed, created and administered by lawyers; it is not a criticism of law as a profession but a general commentary on human nature to observe that it now benefits no one but lawyers. It hurts everyone else. Times change and the current crisis with its skyrocketing insurance premiums; unavailability of insurance coverage; financial extinction of high risk surgical specialties; doctor strikes; and bitter debate between insurance companies, doctors and lawyers is a factual indication that the judicial solution will not change because it cannot. The tort system can no more be reformed to fit modern medical requirements than could a dinosaur be made into a creature suited to the present. The tort system belongs to the history books like covered wagons and knights in armor. The facts speak for themselves; res ipsa loquitur.

Refer to: Schultz AL, Pardee GP, Ensinck JW: Are research subjects really informed? (Informed Consent). West J Med 123:76-80, Jul 1975

Informed
CONSENT

Are Research Subjects Really Informed?

AMELIA L. SCHULTZ, PhD, GERALDINE P. PARDEE, MN, and JOHN W. ENSINCK, MD
Seattle

To determine how adequately patients who participate as subjects for clinical investigation understand their commitment, 50 patients admitted to the Clinical Research Center of the University of Washington were interviewed. Their responses were compared with the detailed statements in the consent forms for the 23 specific protocols under which they were being studied. In spite of careful controls in accord with guidelines of a review committee, only half the patients were able to describe accurately their expectations of the studies to which they had given signed consent.

IN RECENT YEARS there has been increasing concern over the ethics of experimentation on humans. Accordingly, in the United States, the National Institutes of Health, under the Public Health Service of the Department of Health, Education, and Welfare, have set up guidelines for the protection of human research subjects in clinical (that is, biological, behavioral or psychological) research.

To carry out these policies the Human Subjects Review Committee was formed at the University of Washington. Before a research project may be implemented it must be reviewed and the investigators may be required to justify it before the committee.

Our study concerned the criterion of informed consent, the "keystone of the protection of human subjects involved in research."[1] We wished to determine how well patients understood their commitment as research subjects.

Methods

Subjects were randomly selected among patients admitted to hospital for the first time at the Clinical Research Center, a 16-bed facility supported by a grant from the National Institutes of Health. At the time, 100 projects were underway, of which 23 are represented in our sample. All patients consecutively admitted were studied, except that one project was eliminated when it became apparent that further admissions would constitute

From the Departments of Medicine, Nursing and Social Service, University of Washington, Seattle.

This study was conducted through the Clinical Research Center Facility of the University of Washington supported by National Institutes of Health Grant RR-37.

Submitted, revised, May 6, 1975.

Reprint requests to: A. Schultz, PhD, Clinical Research Center, University Hospital, University of Washington, Seattle, WA 98195.

a disproportionately large sample, and five patients were dropped from the sample when we learned that the protocol under which they fell had not come under recent review by the Human Subjects Review Committee.

Within an hour or two of their admission to the Center and their consent interview with the physician-investigator, the subjects were approached and the purpose of this study explained in a brief standard statement. Our questions were based on the following criteria for informed consent stipulated in November, 1971 by the Human Subjects Review Committee from National Institutes of Health guidelines.*

1. A description of the procedures to be followed, including an identification of those which are experimental.
2. A description of the attendant risks and discomforts.
3. A description of the benefits to be expected or the knowledge hoped to be gained.
4. A disclosure of appropriate alternative procedures that might be advantageous to the subject.
5. An offer to answer any inquiries the participant has concerning the experiment.
6. An instruction that the subject is free to withdraw at any time without penalty.
7. An assurance that the subject's identity will remain confidential.
8. A disclosure of what costs the subject may immediately or ultimately be forced to bear and what reimbursement of costs or other compensation he will receive.

Each patient's response to the questions was recorded verbatim by one of the authors and the patient was then given a copy of the questionnaire (Figure 1). To control for observer bias, the first ten interviews were attended also by another of the authors who independently rated the responses. The rank correlation coefficient between the two raters, using Spearman's Rank Correlation Coefficient, was 0.99, which was significant at a point greater than the 1 percent level with 8 degrees of freedom. Since there was thus essential agreement between the raters, subsequent interviews were handled by the first alone and the recorded responses were judged by both simultaneously.

In order to avoid professional bias on the part of the observers, 6 nonmedical, nonhospital-affiliated persons (one anthropologist, one saleswoman, one life insurance underwriter, one social service administrator, two housewives) were asked to rate the responses of ten patients to ten different consent forms, chosen at random from our sample. There were thus 60 judgments.

Twenty-nine scores were exactly the same as those of the original observers, 13 were one step higher or lower, but within one of the two larger categories (adequate or inadequate). Eighteen scores were different: 13 higher, 5 lower. Since this difference of eight (13 percent) did not alter the interpretation of the overall results it seems reasonable to conclude that the scores recorded by the two authors interviewing were not significantly biased by their professional attitudes or their connection with the Clinical Research Center.

Fifty consecutive new patients were studied in a 3½-month period in 1972. (During this time there was a total of 206 admissions.) Forty-one were adult patients, and the parent or parents of nine minors also were interviewed and rated. All were judged to be of normal intelligence and hearing. Forty-nine patients had organic disease, one was a normal control.

Patient Code Number _____

Date _____

1. Are you willing to answer a series of questions relating to how well you understand the form that you have just signed?
2. Why did you volunteer?
3. What are your doctors going to do in the studies?
4. What are they trying to learn?
5. What were you told about the possible risks?
6. What are the benefits of the study?
7. Are any of these procedures experimental?
8. Is there anything in the studies that you are concerned about?
9. Did you refuse to accept any part of the study that was asked of you?
10. Suppose you change your mind about going through with this, what do you think would happen?
11. How do you feel about having the study written up and published in the medical literature?
12. How long will you be here?
13. Who pays for the cost of the study?
14. Are you being paid in any way?
15. If there were complications as the result of any of the procedures who would pay for your care?
16. Have you read the form you signed?
17. Do you have a copy of it?
18. What is the name of the doctor who explained the study to you?
19. Have you any questions about any of these matters?

Figure 1.—Questionnaire Used in Patient Interviews

*Items 1 through 6, Department of Health, Education, and Welfare guidelines, were updated in August 1974, without significant change in the criteria; 7 and 8 were added by the Human Subjects Review Committee.

The analysis was carried out in two ways. First we made an immediate judgment of each patient's overall understanding, which we rated on a four-step scale, based on the type and amount of information obtained from analysis of the first ten interviews. Second, each patient's specific responses were analyzed and rated according to how accurately and thoroughly they reflected statements in the consent form. The consent form was the basis for comparison, since what had otherwise transpired between patient and investigator was not accessible to evaluation.

Results

Table 1 summarizes the overall ratings: 52 percent of all patients were judged to be adequately informed. In retrospect, it appeared that the responses concerning what the investigators were going to *do,* what they were trying to *learn* and what *risks* were likely weighed most heavily in our ratings. Final ratings in two categories, adequate or inadequate, sum up the data most clearly.

The analysis of specific responses is shown in Table 2. Patients were best informed about costs and least well informed about benefits and risks. Such crucial items as procedures, purposes, risks and freedom to withdraw were understood only by about 25 percent of patients, on the average, though consent forms were thorough, specific and detailed on these matters. Table 3 shows that whether patients read the form made no appreciable difference in how well they retained information. Since the policy of the University of Washington's Clinical Research Center requires a patient's signature before any research procedure may be started, the investigator is usually called when the patient arrives and comes to discuss the project and obtain consent. Half the patients come from out of town and many are referred specifically for the research procedures by physicians in the community rather than from within the hospital complex. As a result the consent interview may be the first direct contact between investigator and patient.

Nonspecific benefits are spelled out in 20 out of 23 protocols as "expected," "possibly to be expected" or "not to be expected." In addition, half of the protocols mention specific benefits. Nevertheless, only nine patients (18 percent) understood correctly.

We asked how the patient would feel about publication of the results of the study without mentioning confidentiality as such. Almost without exception they were agreeable or enthusiastic. Only four mentioned that they expected confidentiality.

Regarding freedom to withdraw, 16 patients stated that they could leave the study if they wished. Eighteen others refused to consider the possibility, feeling obligated to follow through.

The item of costs is especially interesting since patients are much clearer on this point than the items stated in the consents. While only 13 out of 23 consents (57 percent) mentioned expenses, 43 out of 50 patients (86 percent) could state cor-

TABLE 1.—*Overall Ratings of Adequacy of Patients' Information*

	Rating	*Number of Patients*
+3	Full, detailed	11
+2	Adequate	15
	Adequately informed	26
+1	Partial	18
0	None, or incorrect	6
	Inadequately informed	24
	TOTAL	50

TABLE 2.—*Analysis of Specific Responses by Items from Human Subjects Review Committee Guidelines*

Guidelines	*Percent of Consents That Specify (Total 23)*	*Percent of Adequately Informed Responses (Total 50)*
Procedures	100	34
Purpose	100	22
Risks	100	20
Confidentiality	91	..
Freedom to withdraw	91	32
Benefits	87	18
Costs	57	86
"Questions answered" or "Adequate explanation given"	39	..
Experimental aspects of procedures*	39	28
Alternative procedures*	4.5	..

*These items do not apply to all consents.

TABLE 3.—*Effect of Reading Consent Form on Patients' Information*

	Number of Patients Adequately Informed	*Number of Patients Inadequately Informed*	*Total*
Form was read	22	17	39
Form read partly or not at all	4	7	11
TOTALS	26	24	50

rectly how they were to be covered. Clearly, many had learned from other sources that they would bear no costs of the research stay in hospital or any complications thereof.

Thirty-two patients (64 percent) understood the length of stay, which 13 out of 23 consent forms (57 percent) spelled out. While no written document requires that investigators specify length of stay it is requested verbally by the Human Subjects Research Committee. Moreover, 57 percent of patients who signed consent forms that did *not* mention length of stay were nevertheless able to state how long they expected to be in hospital and proved to be accurate within 24 hours. Obviously, they had been told. We assume that length of stay is a neutral nonthreatening subject on which doctor and patient can communicate with ease and the fact that there will be no cost is information gladly given and received.

Although it is expected that each subject will be given a copy of the consent form he signed, only ten patients in our sample had in fact received copies and five more had been promised copies. Similarly, the space for the name of a witness was frequently left blank. Such data show the limited policing capabilities of a review committee.

We asked each patient to name the doctor who talked to him. Twenty-two explanations were given by the principal investigator, 11 by an assistant on the project and 12 by a research fellow. It made no difference in the adequacy of patient information: roughly half in each group were adequately informed. Five patients who could not identify the doctor were all inadequately informed in other respects.

In the light of our findings, the inclusion of a statement in a consent form such as "my questions have been answered" does not seem useful. Some patients point out that they did not understand enough to know what questions to ask.

Additional facts came to light which cannot be quantified, but which bear on the matter of consent. Some patients were brought in for brief specific studies which did not require the full protocol, so items in the consent form were crossed out. Others were brought in under the protocol of a research group to which the investigators did not themselves belong, because it was broad enough to encompass the work that was to be done. That is to say, the inflexibility of the present system was met by slightly irregular moves which did not jeopardize the patient but reflect the problems occasioned by practical situations which do not conform to a prearranged system.

Discussion

The discrepancy between the higher overall patient ratings (52 percent adequately informed) and the lower individual response ratings (average 35 percent adequate) requires explanation. Criteria for "adequately informed patient" are obviously less stringent that those for "adequately informed response." A patient may, indeed, accurately anticipate the circumstances of his research stay in hospital, but if his information comes from sources other than the consent form, it will not show as a correct response.

Lack of patient comprehension may be accounted for by the format and content of consent forms, by the timing and manner of presentation and by circumstances in which the patient finds himself. Many consent forms lack clarity, are expressed in complex medical terms difficult for laymen to comprehend. In order to incorporate all items stipulated by the Human Subjects Review Committee, consent forms often become lengthy. Previous studies have shown that the shorter the form, the better the comprehension, and that a document is no substitute for dialogue.[8]

Seven independent judges were asked to rate the consent forms for ease or difficulty of comprehension. Of a total of 70 judgments, 44 (63 percent) were that the forms were easy to understand, 26 (37 percent) that they were hard to understand. Ideally, all should have been easy to understand.

The one-time, after-admission consent interview is far from ideal. Others have pointed out that the earlier the form is presented to the patient, the better[4] and that "consent is not a one-time process."[8]

An important aspect of the consent problem is the life situation in which the patient finds himself and his feelings about it. These can and, judging from patient's comments, frequently do interfere with their comprehension. We found most patients strongly motivated to be at the Clinical Research Center. Asked why they had volunteered, they gave one or more of the following reasons: "to help myself" 38, "to help others" 11, "because my doctor asked me to" 6. The fact that " . . . patients accede to about any request their physicians may make" has been alluded to in previous studies.[11]

Most published discussion of informed consent

is theoretical. To our knowledge, only four references report actual interviews with subjects[3-6] and of these, only two[3,4] are comparable to the present study. The first report, from the Social Service Department of The Clinical Center, Bethesda, in 1954, focused on whether a patient understood the research nature of the admission to hospital. It did not pinpoint his understanding of the specific protocol under which he was admitted. Of 30 patients questioned 66 percent knew that they were research subjects.[4]

The second study was carried out by Pardee in 1964, at the Clinical Research Center, University of Washington. Of ten patients interviewed, half did not know in advance the purpose or the proposed methods of the research for which they were to be admitted; two remained unsure *after* admission to hospital.[3] Our results suggest that 20 years of concern and guidelines[7] have not improved patients' comprehension of the forms that they sign or the accuracy of their expectations as research subjects.[12]

The Human Subjects Review Committee, in addition to evaluating the ethics and potential risks of research, spends much effort in refinement of consent forms without positive results.[7,10] In fact, the very length and complexity of the forms may be a major source of difficulty. In addition, the committee has no practical access to information about actual experience with the forms to insure that the carefully worded documents will be read or understood by the patients. We concur with previously expressed opinions that " . . . written consent unaccompanied by other evidence that explanation has been given, understood, and accepted is of little value . . . "[13]

Suggestions

Growing out of our observations are suggestions, admittedly easier to state than to implement, for improving consent procedures.

- The consent form should be presented at the beginning of the process, when research admission to hospital is first proposed to the patient.[5] It should be left with him to read, consider and discuss with anyone he chooses. After a suitable time interval, and *before* he is admitted to hospital he should be encouraged, in the presence of a witness who has no involvement in the study, to ask questions, and only when both are satisfied, to sign. Arguments have been advanced for the interview to be witnessed by a physician or a nonphysician, or both.[14]
- The consent should consist of a simple blanket form, with headings on all important points from the guidelines, details to be filled in by each investigator. A typical document might be provided as a guide with a nonmedical editor made available to review the final wording.
- The format should cover all essential items, but allow for flexibility in case the progress of the project requires minor changes. This procedure may obviate some of the ad hoc maneuvers that investigators have resorted to.
- If a consent interview were filmed, the words and manner of the participants would become amenable to study and we would have the "other evidence" without which written consent is of little value.[10,13]

REFERENCES

1. Federal Register, 36:221, 1973
2. Ingelfinger FJ: Ethics of experiments on children (Editorial). N Engl J Med 288:791, 1973
3. Pardee GP: A Comparison of Stated Expectations of 10 Selected Patients Prior to and Following Admission on a Research Ward. University of Washington School of Nursing, Seattle, 1964
4. Social Service Department, The Clinical Center: A Study on the Attitude of Patients about Coming to the Clinical Research Center. Bethesda, 1954
5. Alfidi RJ: Informed consent—A study of patient reaction. JAMA 216:1325-1329, 1971
6. Schwartz AH: Children's concepts of research hospitalization. N Engl J Med 287:489-592, 1972
7. Ingelfinger FJ: Informed (but uneducated) consent (Editorial). N Engl J Med 287:465-466, 1972
8. Epstein LC, Lasagna L: Obtaining informed consent: Form or substance. Arch Intern Med 123:682-688, 1969
9. Savard RJ: Serving investigator, patient and community in research studies. Ann N Y Acad of Sci 169, Art 2:429-434, 1970
10. Melmon KL, Grossman M, Morris RC Jr: Emerging assets and liabilities of a committee on human welfare and experimentation. N Engl J Med 282:427-431, 1970
11. Beecher HK: Ethics and clinical research. N Engl J Med 274:1354-1360, 1966
12. Beecher HK: Consent in clinical experimentation: Myth and reality (Editorial). JAMA 195:34, 1966
13. When is consent? (Lead article). Lancet, 7520, Oct 14, 1967

Refer to: Hawes WE: A survey of newborn intensive care centers in California. West J Med 123:81-84, Jul 1975

Special Article

A Survey of Newborn Intensive Care Centers in California

WARREN E. HAWES, MD, MPH, *Berkeley*

Newborn intensive care has come of age in California. Twenty-one newborn intensive care centers and 11 community level units are now approved by Crippled Children Services in California. In 1973 there were more than 6,863 patients admitted to the 20 centers surveyed, over half requiring transport from referring hospitals. This paper provides information on the distribution, admission and occupancy rates, length of stay, costs and admission diagnoses for these high risk infants.

THERE HAVE BEEN increasingly repeated reports of newborn intensive care units (NICU's) being overcrowded and, in some cases, unable to provide space for sick newborn infants. In order to document the actual use and impact of this special service in California a survey of the units was undertaken by the Infant Health Division, Maternal and Child Health Unit, Family Health Services Section, California State Department of Health.

On November 16, 1973, a questionnaire was sent to the 21 Crippled Children Services (CCS) approved newborn intensive care units and to the 11 community (intermediate) level NICU's. By June 13, 1974, all but two centers had responded. The results of the study described here are derived from the information from the 19 responding tertiary NICU's and from one community level center (Valley Medical Center, Fresno) because it has provided most of the services usually included at the tertiary level. The CCS approved NICU's (tertiary) are those considered to provide a full range of services to sick neonates. Intermediate units, due to physical location or lack of certain key personnel in the area, provide a somewhat lesser range of neonatal services and require the backup of a tertiary NICU. The standards for each are delineated by California CCS.

There are, or were during the period of this study, 47 intermediate level intensive care bassinets in community hospitals in California providing, usually, short-term acute care and long-term intermediate level intensive care. The community CCS approved NICU's are distributed as shown in Table 1. Reports from these units have not been included in this report.

Results of Survey

Distribution of NICU Bassinets

There are 404 NICU bassinets available in the 20 centers included in the survey. These beds are distributed as shown in Table 2. Of these beds,

From the Infant Health Division, Maternal and Child Health Unit, Family Health Services Section, California State Department of Health, Berkeley.

Reprint requests to: W. E. Hawes, MD, Chief, Infant Health Division, Maternal and Child Health Unit, Family Health Services Section, California State Department of Health, 2151 Berkeley Way, Berkeley, CA 94704.

ABBREVIATIONS USED IN TEXT

CCS=Crippled Children Services
NICU=Newborn Intensive Care Unit

181 are designated for very sick infants needing 1:1 or 1:2 nurse to patient ratio, 223 are considered as intermediate care beds with 1:3 or 1:4 nurse to patient ratio.

Admissions to NICU's

During the period of the survey, November 1972 through October 1973, there were 6,863 admissions to these 20 NICU's. This represents a mean of 17 admissions per bassinet each year. There were a total of 3,678 transfers (to the 20 respondent NICU's) from outside facilities. During the same period, 3,185 neonates born in the centers with NICU's were transferred into the special care units, as shown in Table 2.

The overall percentage of outside transfers versus inborn admissions is roughly 54 percent outborn to 46 percent inborn. In communities where NICU's have been present longer (such as South Bay and San Francisco), there tends to be a reversal of these figures to 66 percent and 58 percent respectively, being inborn before admission to the NICU.

In calendar year 1973 in California there were approximately 298,000 live births. There were 6,863 admissions to the 20 NICU's plus approximately 1,250 admissions to community NICU's during the 12 months from November 1972 through October 1973, an admission rate of between 2 and 3 per 100 live births per year.

Fifteen of the 20 centers surveyed have maternity services. In calendar year 1973 there were 34,122 live babies delivered in these 15 hospitals (Table 3). During the 12 months of the study, a comparable period, these same hospitals admitted 3,179 of their inborn babies to the NICU's. We therefore estimate that about 9 percent of the babies born in these hospitals require intensive care.

Table 4 shows that an average intensive-care bed surveyed in the study served 17 babies per year. This would suggest a range of need for NICU beds in California from a minimum of 344 to a maximum of 1,548. At present there are over 450 intensive care beds available.

Occupancy Rates

The overall occupancy rate for the NICU's was 87 percent, a noticeably high rate. It was not possible to get a reliable breakdown into acute versus intermediate care rates due to the variety of reporting methods. Also some units do not restrict their beds to a certain level of care but use them interchangeably according to demand. As shown in Table 5, San Diego and the East Bay have a critical bed shortage; South Bay and Orange County are approaching a critical point, while the distribution of occupancy in Los Angeles

TABLE 1.—*Distribution of Community Newborn Intensive Care Units Approved by Crippled Children Services*

Location	*Units*	*Number of Beds*
Northern California (Redding)	1	2
North Coast	2	10
South Bay (San Jose)	1	4
Ventura	1	5
Riverside, San Bernardino	2	11
Los Angeles Metropolitan	2	15
TOTAL	9	47

TABLE 2.—*Number of Beds in Intensive Care Units (ICU) Approved by Crippled Children Services and Number of Admissions into These Units*

Area	*Units*	*Total ICU Bassinets**	*Newborn Admissions*		
			Total	*Transfers*	*Intramural*
Sacramento	1	27	307	197	110
East Bay	2	40	1,042	582	460
San Francisco	3	50	1,006	420	586
South Bay	2	35	967	328	639
Los Angeles	5	145	1,894	1,092	802
Orange County	2	32	426	250	176
San Diego	2	25	492	371	121
San Bernardino-Riverside	1	22	329	199	130
Fresno	2	28	400	239	161
TOTAL CALIFORNIA	20	404	6,863	3,678	3,185

*All levels care.

is very uneven. San Bernardino and San Francisco were still apparently underutilized at the time of the survey.

Length of Stay

The average length of stay in the acute intensive care area was 10.8 days (N=18) and 11.3 days in the intermediate care area (N=16). Twelve centers report that they are returning babies to referral (community) hospitals for convalescent care. The number of returnees was usually unknown, but seven centers reported returning an average of three babies per month.

Cost

The average daily bed charge for acute care (1:1 or 1:2 nurse to patient ratio) was $198 per day (N=20). The range was from a low of $125 to a high of $276.

Intermediate care daily charges average $123 per day. (N=19) The range was from a low of $76 to a high of $175 per day.

TABLE 3.—*Use of Newborn Intensive Care Units (NICU) in Centers Having Maternity Services (Intramural Babies)*

Area (Number of Centers)	*Number of Live Births 1973**	*Rate of Admission to NICU/100 Live Births†*
Sacramento (1)	739	15
East Bay (1)	1,864	24
San Francisco (3)	3,820	15
South Bay (2)	2,949	22
Los Angeles (4)	19,022	4
Orange County (1)	2,139	8
San Diego (1)	738	16
San Bernardino (1)	948	14
Fresno (1)	1,903	8
TOTALS	34,122	9

*January 1, 1973 through December 31, 1973.
†November 1, 1972 through October 31, 1973.

In most cases bed charges did not include ancillary services such as laboratory and x-ray studies. In most cases physician charges were extra also.

Eleven hospitals reported the total overall average cost of infants discharged from their units. The average total cost was computed to be $5,178.

Types of Cases Admitted to NICU's

An average of 41 percent of the newborns admitted had a diagnosis of respiratory distress syndrome. The range was from 15 percent to 90 percent in the 20 hospitals. Hospitals reported congenital anomalies, Rh hemolytic disease and sepsis as the next most frequent diagnoses.

Prematurity, "small-for-dates," meconium aspiration, metabolic disorders, hyperbilirubinemia (including ABO blood groups incompatability) pneumothorax, infant of diabetic mother were diagnoses for a substantial number of the remaining babies admitted to these units.

Neonatal Mortality

There was a great deal of misunderstanding and error in presenting neonatal mortality figures. Four hospitals presented them in percent rather than in conventionally accepted rates per 1,000 live births.

We were able to compare the 1970 and 1971 figures with the California vital statistics data from the linked birth-death tapes. Fifteen units are in hospitals with newborn services. In 1970, 11 of the 15 varied more than one death per 1,000 live births with the State's statistics. Five differed more than five deaths per 1,000 live births. In 1971, ten hospitals varied more than one per 1,000 live births and five differed more than five deaths per 1,000 live births. In 1970, five of the reporting

TABLE 4.—*Admission Rates for Newborn Intensive Care Unit Beds (November 1972 through October 1973)*

		Number of Admissions per Year, per Bassinet				
		Outborn		*Inborn*		
Area (Number of Centers)	*Total No. Bassinets*	*Number*	*Percent*	*Number*	*Percent*	*Total*
Sacramento (1)	27	7.3	64	4.1	36	11.4
East Bay (2)	40	14.6	56	11.5	44	26.0
San Francisco (3)	50	8.4	42	11.7	58	20.1
South Bay (2)	35	9.4	34	18.3	66	27.6
Los Angeles (5)	145	7.5	58	5.5	42	13.1
Orange County (2)	32	7.8	59	5.5	41	13.3
San Diego (2)	25	14.8	75	4.8	25	19.7
San Bernardino-Riverside (1)	22	9.0	60	5.9	40	15.0
Fresno (2)	28	8.5	60	5.8	40	14.3
TOTAL CALIFORNIA (20)	404	9.1	54	7.9	46	17.0

hospitals had higher neonatal death rates, one had the same and nine had lower rates than the State's vital statistics records. In 1971, seven hospitals reported higher figures, three the same and five were lower than the State's statistics.

Neonatal mortality figures as kept by hospital records are generally not accurate. One explanation is that some reports of deaths occurring before 28 days of age are not made by the hospital of birth because the infants had been discharged and died elsewhere. If this explanation were correct, the hospital's figures should all be lower than the vital records, and this is not the case in this survey. This does point out the need for better methods of keeping statistics.

Outcome

The outcome for all newborns admitted to Newborn Intensive Care Units ranged from 50 percent to 96.3 percent recovery of inborn babies (N=15), and from 44 percent to 98 percent recovery of outborn babies (N=21). The average recovery of inborns was 84.4 percent and of outborns was 73.5 percent. This is a significant difference. The data were not available to break this down by outcome for gestational age and weight which could have made the information more useful.

TABLE 5.—*Occupancy Rates for California Newborn Intensive Care Units' Intensive and Intermediate Care* (November 1972 through October 1973)*

Area (Number of Centers)	*Average Occupancy Rate (%)*	*Range (%)*
Sacramento (1)†	83	..
East Bay (2)	139	77-160
San Francisco (3)	64	57- 67
South Bay (2)	88	77- 96
Los Angeles (5)	74	45-109
Orange County (2)	87	83- 95
San Diego (2)	104	100-106
San Bernardino-Riverside (1)	57	..
Fresno (2)	75	74- 76
TOTAL CALIFORNIA (20)	87	

*Based on best estimates available.
†Intensive care only.

TABLE 6.—*Diagnoses of Cases Admitted*

Diagnoses	*Percent*	*Number of Hospitals Reporting*
Respiratory distress	41.3	20
Congenital anomalies	11.4	19
Sepsis	8.4	19
Rh hemolytic disease	3.0	18

Summary

There are over 450 newborn intensive care beds available in California hospitals. Over 400 of these are in tertiary units providing total care for sick newborns. At the present time there is a NICU bed shortage in some areas of the state, the units running at an occupancy rate of over 87 percent. The bed situation is particularly critical in the East Bay and San Diego. Assembly Bill 4439 (Green and Lanterman) signed by the Governor on September 23, 1974, offers funding for two infant medical dispatch centers for NICU bed availability. When this service is functioning the physician needing an intensive care bed for a sick newborn infant will only need to make one phone call to locate an empty bed and initiate the transfer process. The survey suggests that from 2 to 9 percent of newborns need intensive care. The present bed availability is ample for the lower figure but insufficient to meet the upper one.

The cost of newborn intensive care is high, daily rates averaged $198 per day and $123 per day for intermediate care, total costs averaging $5,178 per baby. The total cost of NICU care in the 20 units is in excess of 35 million dollars annually.

Respiratory distress syndrome was the reason for NICU admission in more than 40 percent of the cases. Congenital anomalies and sepsis were next, accounting for approximately 20 percent of the admissions.

It is clear that the recovery rate in these units is very high, averaging 84.4 percent for inborn babies and 73.5 percent for transferred babies. Reductions in mortality rates generally reflect parallel reductions in morbidity rates. It is essential to provide adequate bed space in special neonatal care centers for all sick neonates until more can be done to reduce their number.

in memoriam

Adler, Ethel (Ethel Adler Hurwitz), San Leandro. Died May 3, 1975 in San Leandro of cancer, aged 60. Graduate of the University of Nebraska College of Medicine, Omaha, 1942. Licensed in California in 1946. Dr. Adler was a member of the Alameda-Contra Costa Medical Association.

Anderson, William Thayer, Anaheim. Died May 11, 1975 in Anaheim, aged 52. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1951. Licensed in California in 1955. Dr. Anderson was a member of the Orange County Medical Association.

Babington, Suren H., Berkeley. Died May 8, 1975 in Berkeley of cancer, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Babington was a retired member of the Alameda-Contra Costa Medical Association.

Benzinger, Martin, Alameda. Died April 19, 1975 in Alameda, aged 82. Graduate of the University of Cincinnati College of Medicine, 1918. Licensed in California in 1919. Dr. Benzinger was a member of the Alameda-Contra Costa Medical Association.

Christensen, Valdemar E., Topanga. Died March 16, 1975 of heart disease, aged 43. Graduate of the College of Physicians and Surgeons, Los Angeles, 1960. Licensed in California in 1961. MD degree from California College of Medicine, 1962. Dr. Christensen was a member of the Los Angeles County Medical Association.

Coman, Charles P., Los Angeles. Died April 29, 1975 in Los Angeles, aged 55. Graduate of the University of Southern California School of Medicine, Los Angeles, 1947. Licensed in California in 1947. Dr. Coman was a member of the Los Angeles County Medical Association.

Durgin, Rubie Mae (Rubie Mae Durgin McKinne), Berkeley. Died May 26, 1975 in Oakland of acute localized peritonitis, aged 82. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1917. Licensed in California in 1917. Dr. Durgin was a retired member of the Alameda-Contra Costa Medical Association.

Edwards, Charles Frederick, Glendale. Died March 2, 1975 in Glendale of ruptured abdominal aortic aneurysm, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, 1939. Licensed in California in 1939. MD degree from California College of Medicine, 1962. Dr. Edwards was a member of the Los Angeles County Medical Association.

Frey, Russell Gregory, Red Bluff. Died April 2, 1975 in Red Bluff, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Frey was a member of the Tehama County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.

Harris, Harold Isadore, Los Angeles. Died May 3, 1975 in Los Angeles, aged 81. Graduate of Baylor University College of Medicine, Houston, 1926. Licensed in California in 1926. Dr. Harris was a member of the Los Angeles County Medical Association.

Herzikoff, Sam Sidney, Los Angeles. Died March 30, 1975 in Los Angeles of leukemia, aged 77. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1919. Licensed in California in 1919. Dr. Herzikoff was a member of the Los Angeles County Medical Association.

Hoffman, Philip B., Marysville. Died April 22, 1975 in Yuba City, aged 83. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1917. Licensed in California in 1917. Dr. Hoffman was a retired member of the Yuba-Sutter-Colusa County Medical Society.

Holland, Frank F., North Hollywood. Died March 19, 1975 in Sherman Oaks of carcinoma of the stomach with metastases to esophagus and liver, aged 60. Graduate of St. Louis University School of Medicine, 1939. Licensed in California in 1946. Dr. Holland was a member of the Los Angeles County Medical Association.

Jones, J. Roy, Sacramento. Died May 30, 1975 in San Francisco, aged 86. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Dr. Jones was a retired member of the Sacramento Medical Association.

Kidwell, Thomas Thurman, Madera. Died April 23, 1975, aged 59. Graduate of Loyola University of Chicago, Stritch School of Medicine, 1950. Licensed in California in 1962. Dr. Kidwell was a member of the Fresno County Medical Society.

Kilfoy, Edward Joseph, Los Angeles. Died May 12, 1975 in West Los Angeles of heart disease, aged 78. Graduate of St. Louis University School of Medicine, 1922. Licensed in California in 1926. Dr. Kilfoy was a member of the Los Angeles County Medical Association.

Kottke, Elmer E., Palm Springs. Died December 2, 1974 in Palm Springs, aged 75. Graduate of Northwestern University Medical School, Chicago, 1928. Licensed in California in 1944. Dr. Kottke was a member of the Los Angeles County Medical Association.

KULLY, BARNEY M., Los Angeles. Died April 16, 1975 in Los Angeles of heart disease, aged 78. Graduate of the Creighton University School of Medicine, Omaha, 1917. Licensed in California in 1935. Dr. Kully was a member of the Los Angeles County Medical Association.

LICHTY, JOHN M., San Diego. Died May 4, 1975, aged 79. Graduate of the University of Pittsburgh School of Medicine, 1923. Licensed in California in 1943. Dr. Lichty was a member of the San Diego County Medical Society.

LOVELY, JAMES PHILLIP, SR., San Jose. Died May 6, 1975 in San Jose, aged 77. Graduate of the Creighton University School of Medicine, Omaha, 1923. Licensed in California in 1924. Dr. Lovely was a retired member of the Santa Clara County Medical Society.

MAGID, GEORGE JOSEPH, Santa Clara. Died April 27, 1975 in Stanford of heart disease, aged 54. Graduate of the Chicago Medical School, 1952. Licensed in California in 1955. Dr. Magid was a member of the Santa Clara County Medical Society.

MCGUINNESS, JOSEPH STANLEY, San Francisco. Died May 22, 1975 in San Francisco, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. McGuinness was an associate member of the San Francisco Medical Society.

O'FARRELL, NORMAN MORRIS, San Diego. Died April 6, 1975 in a plane crash near Alpine, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1936. Licensed in California in 1936. Dr. O'Farrell was a member of the San Diego County Medical Society.

POWERS, HARRY JAMES, Carmel. Died April 3, 1975, aged 78. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1921. Licensed in California in 1921. Dr. Powers was a retired member of the San Bernardino County Medical Society.

PUTNAM, TRACY J., Beverly Hills. Died March 29, 1975 in Los Angeles of leukemia, aged 80. Graduate of Harvard Medical School, Boston, 1920. Licensed in California in 1946. Dr. Putnam was a member of the Los Angeles County Medical Association.

QUARRY, PAUL THOMAS, Santa Rosa. Died April 7, 1975 in Santa Rosa, aged 76. Graduate of the University of Michigan Medical School, Ann Arbor, 1923. Licensed in California in 1924. Dr. Quarry was a retired member of the Sonoma County Medical Association.

REITHMAYER, EDWIN N., San Diego. Died April 24, 1975 in San Diego, aged 61. Graduate of Hahnemann Medical College & Hospital of Philadelphia, 1942. Licensed in California in 1945. Dr. Reithmayer was a member of the San Diego County Medical Society.

SETTLE, FRANCIS BOAS, Seal Beach. Died February 26, 1975 in Garden Grove of cerebral thrombosis, aged 83. Graduate of St. Louis University School of Medicine, 1918. Licensed in California in 1921. Dr. Settle was a member of the Los Angeles County Medical Association.

WATERS, WAYNE WALTER, Los Angeles. Died May 4, 1975, aged 62. Graduate of Marquette University School of Medicine, Milwaukee, 1941. Licensd in California in 1941. Dr. Waters was a member of the Los Angeles County Medical Association.

THE WESTERN
Journal of Medicine

Refer to: Jawetz E: Synergism and antagonism among antimicrobial drugs—A personal perspective. West J Med 123: 87-91, Aug 1975

Synergism and Antagonism Among Antimicrobial Drugs

A Personal Perspective

ERNEST JAWETZ, MD, PhD, *San Francisco*

I APPRECIATE the opportunity to speak to you to honor the memory of Dr. Henry Brainerd. I knew Hank Brainerd for 25 years, from my first contact with him as a student on the Infectious Disease Service of the San Francisco City and County Hospital in 1944 to his untimely death in 1969. Hank was an accomplished bedside clinician and teacher. I believe that he truly enjoyed both the challenge and his own mastery of clinical medicine. He was also deeply devoted to the University of California, where he spent his entire academic career. I believe that he was often frustrated by the endless demands of academic administration, yet he was too conscientious to shrug them off. This conflict may well have contributed to the illness that caused his early and tragic death. Hank Brainerd will be remembered by students and associates for his unfailing kindness and courtesy and his eternal willingness to help others, as well as to serve his patients.

A Baffling Case

As a topic for this talk, I have chosen an area in which Hank and I collaborated for many years —antibiotic synergism and antagonism. Looking over our papers[1] brought back some recollections which I propose to share with you. About a quarter century ago, a baffling case was presented to Dr. Brainerd (Chart 1). The patient was a 38-year-old woman in the third month of pregnancy who had a history of rheumatic fever in childhood. Because of the signs of mitral stenosis, a therapeutic abortion was carried out in April 1948. Soon after, fever and signs of infective endocarditis developed, and blood cultures yielded Streptococcus faecalis, inhibited *in vitro* by 8 units per ml of penicillin. Initial treatment with penicillin G (10 million units daily for 33 days) produced pronounced clinical improvement, but bacteriological relapse occurred soon after therapy was stopped. This sequence repeated itself with courses of chlortetracycline (6 grams daily for 30 days) and penicillin G (100 million units daily for 30 days—a total of 1,800 grams). During treatment, levels of penicillin in the blood repeatedly exceeded 1,000 units per ml. In spite of additional therapy and splenectomy because of a suspected abscess, the patient's condition deteriorated gradually, hemiplegia developed and the patient died late in 1949. Blood cultures were positive for the same organism, of the same sensitivity to penicillin, whenever the patient was not receiving antibacterial drugs.[2]

During the five years preceding this patient's presentation, hundreds of other cases of endocarditis had been cured with penicillin. Why did treatment of this patient fail in spite of the extra-

The third annual Henry Brainerd Memorial Lecture, given at San Francisco General Hospital on April 29, 1975.

The author is Chairman and Professor, Department of Microbiology, and Professor, Department of Medicine, University of California, San Francisco.

Reprint requests to: E. Jawetz, MD, PhD, Chairman, Department of Microbiology, University of California, San Francisco, San Francisco, CA 94143.

ordinary amounts of drugs administered—amounts which had produced drug levels in the blood often 100 times higher than required to inhibit the organisms *in vitro?* Might inhibition of bacterial growth not be sufficient to cure endocarditis? Several principally bacteriostatic drugs like tetracyclines and chloramphenicol regularly failed to cure endocarditis. In attempts to find answers to these questions, we decided to explore the bactericidal action of single drugs and drugs in combinations. An example of the results obtained with enterococci is shown in Chart 2. Penicillin alone was inhibitory, and in combination with streptomycin (which by itself had no effect in that concentration) it was rapidly bactericidal—an apparent beneficial effect of a drug combination, possibly synergism. However, the addition of chloramphenicol to penicillin greatly diminished the bactericidal effect, apparent antagonism.[2]

Drug Combinations

At the same time as test-tube experiments showed enhanced killing of enterococci by the combination of penicillin with streptomycin, many patients were cured by this combination, whereas single drugs had failed. This success stimulated widespread experimentation with many drug mixtures and many microorganisms, especially those that often exhibited resistance to single drugs. Staphylococcal disease caused by penicillinase-producing organisms became rampant in the 1950's, and thus it was a welcome observation that some drug pairs could eradicate such staphylococci.[1,3] Endocarditis caused by penicillinase-

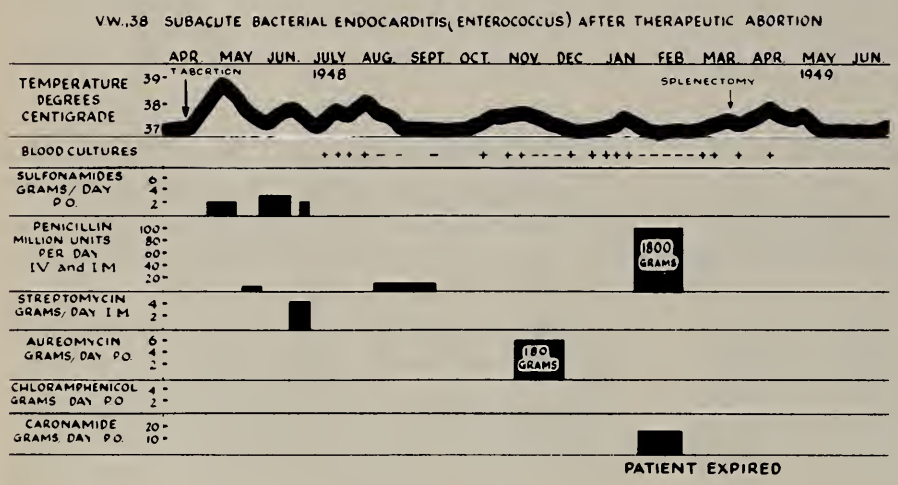


Chart 1.—Patient with endocarditis caused by Strepococcus faecalis with several relapses and ultimate death, following courses of bacteriostatic drugs in large amounts.

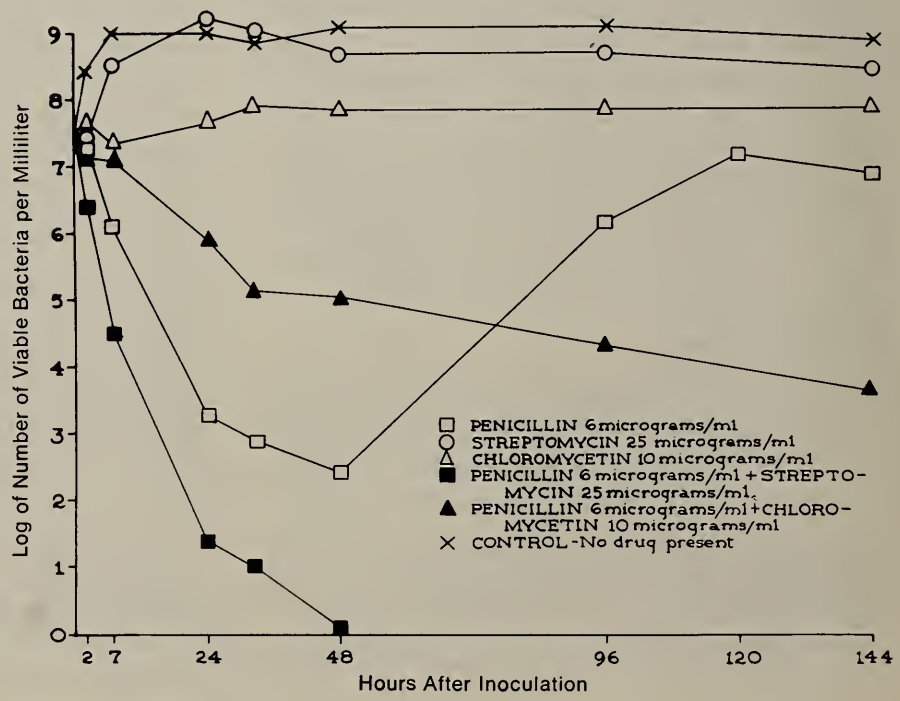


Chart 2.—The effects of penicillin (6 μg per ml), streptomycin (25 μg per ml) and chloramphenicol (10 μg per ml), singly and in combination, on a strain of Streptococcus faecalis *in vitro*.

producing staphylococci had a high mortality when penicillin alone was used. By contrast, Dr. Brainerd and I could document bacteriologic cure in 11 of 14 (78 percent) such patients, treated with carefully selected bactericidal drug combinations—long before the advent of beta-lactamase-resistant penicillins. This feat is now only of historical interest, but it illustrates the therapeutic potential that combined antimicrobial therapy might hold.

Enthusiasm for drug combinations grew steadily. Among organisms causing Gram-negative sepsis, laboratory tests often showed enhanced killing by drug mixtures.[4] Pharmaceutical manufacturers busily compounded antibiotic combinations, and advertisements promised virtual infallibility for these mixtures. Physicians were persuaded by these arguments and prescribed millions of doses of such fixed combinations. The stocks of drug firms skyrocketed. These developments were described by the then director of the antibiotic division of the Food and Drug Administration, Dr. Henry Welch, as follows: " . . . a new and powerful trend is growing in anti-infectious therapy; the use of antibiotics in combination, the replacement of single 'magic bullets' by a barrage of chemotherapeutic agents. . . . "[5]

Only a small group of physicians concerned with infectious diseases tried to stem this tide. Dr. Brainerd and colleagues[6] wrote editorials decrying the misuse of fixed antibiotic combinations, and Drs. Dowling and Finland[7] marshalled some friends to similar protest action. Among the disadvantages of antimicrobial combinations which were widely discussed was the possible occurrence of antibiotic antagonism. In many laboratory tests it had been apparent that the bactericidal action of a penicillin or of an aminoglycoside was diminished by the presence of such inhibitors of protein synthesis as tetracycline or chloramphenicol. Animal experiments confirmed the possibility of antagonism *in vivo,* and its occurrence in man was shown by Lepper and Dowling.[8] In pneumococcal meningitis treated with penicillin alone, the mortality was 30 percent, but when chlortetracycline was administered together with the same amount of penicillin, the mortality rose to 79 percent. Other clinical studies confirmed the possibility of antagonism in clinical situations.

The panels of experts appointed by the National Academy of Sciences-National Research Council (NAS-NRC) to evaluate the safety and efficacy of drugs addressed themselves also to antimicrobials. Under the vigorous leadership of Dr. C. Kunin, the NRC panels condemned the indiscriminate use of antibiotics and formally spoke out against fixed antimicrobial combinations.[9] The Food and Drug Administration (FDA) endorsed this position and the sale of fixed antimicrobial combinations ceased in the United States, although it flourished in other countries. The issue was reopened once again with the advent of sulfonamide-trimethoprim mixtures,[10] and at present we are witnessing greatly increasing concern with antimicrobial combinations, as evidenced by the large number of publications in the field which are rediscovering the phenomena of synergism and antagonism and applying them to new model systems.[11] I believe that the following mathematical relationship may apply: Popularity of studying drug combinations equals increase in drug resistant bugs divided by success of treatment with single drugs.

Based on this brief survey of the past, I must conclude that the only thing we learn from history is that we never learn from history. Therefore, I now wish to turn to some of the clearly established features of antimicrobial drug antagonism and synergism and attempt to define their clinical implications.

Antagonism

According to a classical isobologram (Figure 1), any combined effect of two drugs that is smaller than the sum of the effects of each single

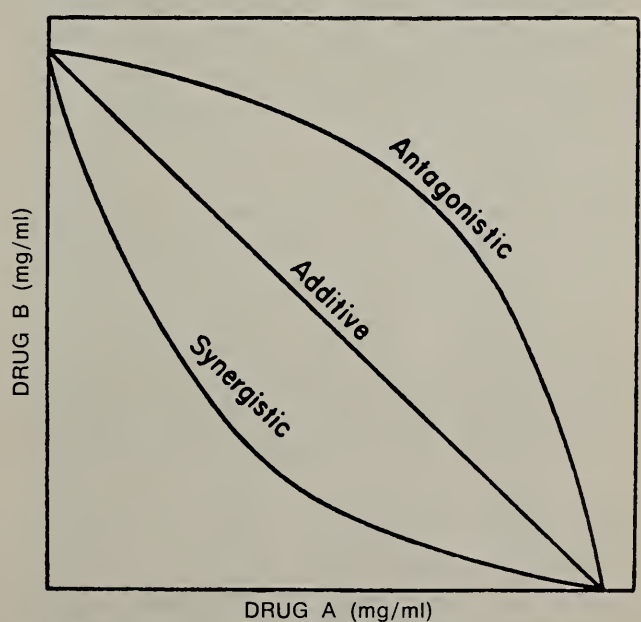


Figure 1.—Isobologram describing additive, synergistic and antagonistic actions of two drugs acting simultaneously on a homogeneous microbial population.

drug present in the mixture may be termed antagonism. Antagonism might be evidenced as a decrease in bacteriostatic or bactericidal action *in vitro* or in the curative effect *in vivo*.[2] Many difficulties exist in translating *in vitro* results into clinical meaning. Hundreds of examples illustrate an apparent antagonistic effect *in vitro,* even when physical inactivation of one drug by another (for example, in mixtures of gentamicin and carbenicillin) is ruled out. The most striking features of antagonism are: (A) it is most pronounced when bactericidal action is involved; (B) the interfering drug must be present in a biologically active, but not of itself curative, amount; (C) the interfering drug should be present before, or at the same time as, the bactericidal drug exerts its effect; (D) a large excess of the interfering drug may obscure or overcome the antagonistic effect.

Antagonism has been seen in a variety of animal models. A striking example of the need for bactericidal action was the magnitude of antagonism observed in neutropenic mice, but not normal mice subjected to infection.[12] Antagonism is more easily shown with single dose treatments (which permit a simple relationship between the interfering and the effective drug) than in multiple dose treatment when levels of drug vary constantly. This may well be one reason for the scarcity of documented antagonism in clinical therapy, where multiple dose treatment is the rule. Another reason may be the relative ease with which an excess of the interfering drug can overcome antagonism. In human therapy, excessive doses (that is, doses more than those of minimal biologic activity) are the rule. Because of these limitations it is my belief that while antagonism may occur in clinical therapy, it is rarely seen as the end result of such therapy, namely, a significant increase in treatment failures. Meningitis may be an exception, and it is there that the most convincing, statistically significant examples of antagonism have been documented.[13] In view of these considerations, I question the clinical relevance of the many recent studies which reiterate the occurrence of antagonism *in vitro* among several more recent arrivals on the antimicrobial drug market. The mechanism of antagonism remains speculative: Most antagonizing drugs are inhibitors of protein synthesis, and they can inhibit drugs which block cell wall synthesis (for example, penicillins, or drugs which block protein synthesis, such as aminoglycosides). Perhaps antagonism occurs when microbial metabolism is slowed by bacteriostatic drugs in situations that require fully active metabolism for maximum bactericidal effect.

Synergism

At least three mechanisms are known by which one drug greatly enhances the antibacterial activity of another.[14] The first is the blocking of successive steps in a metabolic sequence essential for microbial growth. The leading example is seen in the mixture of sulfonamide—which inhibits para-aminobenzoic acid (PABA) uptake—and trimethoprim—which inhibits dihydrofolate reductase.

The second mechanism consists of one drug (such as methicillin) inhibiting an enzyme (beta-lactamase from Gram-negative bacteria), capable of destroying the second drug (such as ampicillin). This mechanism has been studied in detail by Sabath,[15] but it suffers from so many limitations that, in my opinion, its practical importance is small.

The third mechanism, and the one most extensively studied, is based on the ability of cell-wall inhibitors to enhance the passage of other drugs into the cytoplasm of the bacterial cell and permit them to reach lethal concentrations on ribosomes. For example, enterococci exhibit a relative permeability barrier to aminoglycosides. When penicillins are present, the entry of aminoglycoside is facilitated, and ribosomal protein synthesis is blocked with a lethal effect on the bacteria. This has been suggested some decades ago in the demonstration of penicillin-streptomycin[2] and was proven recently much more elegantly with radioactively labeled aminoglycoside by Moellering.[16] Susceptibility to this type of synergistic mechanism can be determined by simple laboratory determination of ribosomal susceptibility of the organism to a given aminoglycoside.[17] Thus it may be tested early whether enterococcal endocarditis is likely to be cured by a penicillin with streptomycin, or whether kanamycin or gentamicin will be required.

This third mechanism of synergism is not limited to enterococci. Viridans streptococci may be killed much faster by a penicillin-aminoglycoside combination than by the penicillin alone,[18,19] and this may also apply to staphylococci.[1-3] Gram-negative bacteria may be susceptible to mixtures of an aminoglycoside with a cell-wall inhibitor such as a cephalosporin, ampicillin or carbenicillin.[4,20] This effect has been shown most convincingly in Gram-negative sepsis of neutropenic patients immunosuppressed by cancer chemotherapy.[21]

Practical Considerations in the Use of Drug Combinations

While doctors are, in general, quite satisfied with the clinical efficacy of antimicrobials, rumors of drug resistance and treatment failure introduce a feeling of insecurity. The thought then occurs: If one drug is good, two should be better and three should cure practically everybody of everything. This emotional response often leads to the administration of drug combinations. Let us briefly list some outstanding advantages, and some disadvantages, of this approach.[19]

Advantages

- Prompt treatment of a desperately ill patient suspected of having a serious infection. Two or more drugs are aimed at the most likely pathogens. This may be particularly important in the immunodeficient host.
- The emergence of microbial mutants resistant to one drug may be greatly delayed by the simultaneous presence of a non-cross-reacting second drug. This applies particularly to chronic infections with large microbial populations as in tuberculosis. It has been suggested that occasionally fungal infections may also be benefited—for example, by combined use of fluorocytosine and amphotericin B.[22]
- True mixed infections of blood stream—a rarity.
- The desire to achieve bactericidal synergism as discussed above—a very rare event unless a specific drug pair can be tailor-made and fitted to a specific microbial pathogen.

Disadvantages

- False sense of security. If a physician is already prescribing several antimicrobials, his zeal for achieving a specific etiologic diagnosis is greatly diminished.
- The more drugs that are given simultaneously, the greater is the chance for sensitization of the patient or for toxic and hypersensitivity reactions.
- Unnecessarily high cost.
- In most instances, a combination of drugs is no more effective than its single most effective member.

Although these and other disadvantages have been reiterated many times, reviews of treatment programs show that antimicrobial drugs continue to be used in combination far more often than can be justified. Perhaps we should recall the statement of a famous physician written 800 years ago:[23] "If one can manage well with one individual drug, one should not use a compound one. . . . One should use medications compounded of multiple ingredients only when compelled to do so." May I express the pious hope that my presentation may help physicians to feel compelled less often to use antimicrobial combinations.

REFERENCES

1. Jawetz E, Brainerd HD: Staphylococcal endocarditis—Results of combined antibiotic therapy in fourteen consecutive cases (1956-1959). Am J Med 32:17-24, 1962
2. Jawetz E: Antibiotic synergism and antagonism—A review of experimental evidence (Almroth Wright Lecture, 1952). Arch Intern Med 90:301-309, 1952
3. Jawetz E: Combined antibiotic therapy in serious infections caused by drug-resistant staphylococci (1956-1957). Arch Intern Med 103:289-307, 1959
4. Klastersky J, Cappel R, Daneau D: Clinical significance of in vitro synergism between antibiotics in gram-negative infections. Antimicrob Agents Chemother 2:470-475, 1972
5. Welch H: A rational approach to combined antibiotic therapy. Antibiot Med Clin Therapy 3:375-377, 1956
6. Brainerd HD, Jawetz E, Rantz LA: Fixed antibiotic combinations (Editorial). Calif Med 86:56-57, 1957
7. Dowling HF, Finland M, Hamburger M, et al: The clinical use of antibiotics in combination. Arch Intern Med 99:536-538, 1957
8. Lepper MH, Dowling HF: Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin—Studies including observations on an apparent antagonism between penicillin and aureomycin. Arch Intern Med 88:489-494, 1951
9. NAS-NRC Division of Medical Sciences—Drug Efficacy Study: Fixed combinations of antimicrobial agents. N Engl J Med 280:1149-1154, 1969
10. Rosenblatt JE, Stewart PR: Combined activity of sulfamethoxazole, trimethoprim, and polymyxin B against gram-negative bacilli. Antimicrob Agents Chemother 6:84-92, 1974
11. Wallace JF, Smith RH, Garcia M, et al: Antagonism between penicillin and chloramphenicol in experimental pneumococcal meningitis. J Lab Clin Med 70:408-418, 1967
12. Sande MA, Overton JW: In vivo antagonism between gentamicin and chloramphenicol in neutropenic mice. J Infect Dis 128: 247-250, 1973
13. Mathies AW Jr, Leedom JM, Ivler D, et al: Antibiotic antagonism in bacterial meningitis. Antimicrob Agents Chemother 218-224, 1967
14. Jawetz E: Combined actions of antimicrobial drugs. *In* Gillette JR, Mitchell JR (Eds): Concepts in Biochemical Pharmacology (Handbook of Experimental Pharmacology). Vol. 28, Part 3. Springer-Verlag, New York, 1975, pp 343-358
15. Sabath LD: Synergy of antibacterial substances by apparently known mechanisms. Antimicrob Agents Chemother 210-217, 1967
16. Moellering RC Jr, Weinberg AN: Studies on antibiotic synergism against enterococci—II. Effect of various antibiotics on the uptake of ^{14}C-labeled streptomycin by enterococci. J Clin Invest 50:2580-2584, 1971
17. Standiford HD, de Maine JB, Kirby WMM: Antibiotic synergism of enterococci. Arch Intern Med 126:255-259, 1970
18. Durack DT, Pelletier LL, Petersdorf RG: Chemotherapy of experimental streptococcal endocarditis—II. Synergism between penicillin and streptomycin against penicillin-sensitive streptococci. J Clin Invest 53:829-833, 1974
19. Jawetz E: The use of combinations of antimicrobial drugs. Ann Rev Pharmacol 8:151-170, 1968
20. Bryan CS, Marney SR, Alford RH, et al: Gram-negative bacillary endocarditis—Interpretation of the serum bactericidal test. Am J Med 58:209-215, 1975
21. Klastersky J, Henry A, Hensgens C, et al: Gram-negative infections in cancer—Study of empiric therapy comparing carbenicillin-cephalothin with and without gentamicin. JAMA 227:45-48, 1974
22. Rabinovich S, Shaw BD, Bryant T, et al: Effect of 5-fluorocytosine and amphotericin B on *Candida albicans* infection in mice. J Infect Dis 130:28-31, 1974
23. ben Maimon Rabbi M: The Preservation of Youth. New York, Philosophical Library, 1958

Refer to: DeLong WB: The diagnostic pitfalls of subarachnoid hemorrhage from intracranial aneurysms. West J Med 123:92-100, Aug 1975

The Diagnostic Pitfalls of Subarachnoid Hemorrhage from Intracranial Aneurysms

W. BRADFORD DeLONG, MD, *San Francisco*

The subtle manner in which subarachnoid hemorrhage frequently presents may delay appropriate treatment. The patient may deteriorate and die from aneurysmal rebleeding or from cerebral ischemia associated with vasospasm before the true nature of the disease is recognized. Five patients are described in whom subarachnoid hemorrhage was initially not recognized. Pitfalls in diagnosis are discussed, and an outline is presented for the evaluation of patients suspected of harboring ruptured intracranial aneurysms.

THE OUTLOOK for patients with ruptured intracranial aneurysms is improving. Yasargil, using microsurgical techniques, has achieved the remarkably low operative mortality of 1.9 percent in the 373 patients he operated upon from January 1970 through July 1974.[1] The use of antifibrinolytic agents is being investigated.[2,3] These agents inhibit clot lysis, and theoretically encourage the formation and preservation of a firm blood clot within and around a ruptured aneurysm, thus reducing the risk of rebleeding. This may prove to be a valuable form of therapy, used either alone or as an adjunct to surgical obliteration of the aneurysm.

From the Saint Francis Memorial Hospital, San Francisco, and the Department of Neurosurgery, University of California, San Francisco.

Submitted, revised, March 21, 1975.

Reprint requests to: W. Bradford DeLong, MD, 4141 Geary Boulevard, Suite 425, San Francisco, CA 94118.

Slosberg champions an aggressive nonsurgical hypotensive regimen in the treatment of intracranial aneurysms.[4] Though many neurosurgeons are skeptical of the safety of Slosberg's approach, his work has certainly emphasized the importance of careful monitoring of blood pressure and control of hypertension in the acute and chronic management of the patient who harbors an intracranial aneurysm.

Stereotactic methods under development allow the obliteration of aneurysms without open craniotomy,[5,6] and Serbinenko has been successful in catheterizing specific intracranial arteries selectively.[7] Refinement of his methods may make possible the obliteration of aneurysms with little more risk than that of cerebral angiography.

As the treatment of ruptured intracranial aneurysms improves, it becomes more and more im-

portant to institute appropriate therapy as soon as possible, but it is surprising how often subarachnoid hemorrhage is misdiagnosed.[8] Inappropriate measures which may actually harm the patient are instituted, and appropriate measures are inadvertently withheld. It is relatively easy to recognize subarachnoid hemorrhage in a young or middle-aged patient presenting with a history of sudden headache followed by stiff neck, lethargy, hemiparesis or seizures. However, subarachnoid hemorrhage frequently presents in a more subtle form. It is exceedingly important that these subtle variations be recognized and therapy instituted before the patient deteriorates from rebleeding or cerebral ischemia associated with vasospasm.

This author has seen a number of patients with subarachnoid hemorrhage and in whom clinical features were at first confusing. The following patients are examples. They were all first seen by well trained, experienced, conscientious physicians. The diagnostic pitfalls these doctors encountered illustrate that in order to avoid misdiagnosing subarachnoid hemorrhage, a physician's index of suspicion must frequently be very high.

Reports of Cases

Case 1. A 50-year-old woman reported that an "exploding" headache had suddenly developed one evening after she ate a lobster dinner. The patient induced vomiting to relieve severe nausea which developed immediately following the onset of the headache. In a hospital emergency room, a history of migraine headaches was given, though there had been no significant headaches during the five years preceding the present illness. There was no history of hypertension. The patient was neurologically normal. It is not known if there was nuchal rigidity. The patient was told that blood pressure was elevated, and a diagnosis of hypertensive headache was made. Consideration was also given to a diagnosis of acute gastroenteritis secondary to the ingestion of contaminated shellfish. Two injections (presumably of antihypertensive medication) were given and the patient was sent home with an antiemetic. The symptoms persisted and four days later an internist was consulted and he admitted the patient to hospital. At that time, there was nuchal rigidity and the patient was somewhat lethargic but oriented. Deep tendon reflexes were hyperactive on the left. Blood pressure varied between 140/80 and 170/90 mm of mercury.

On lumbar puncture, bloody cerebrospinal fluid was found with a supernatant that was notably xanthochromic. On transfemoral catheter cerebral angiography, a right internal carotid artery aneurysm was noted at the origin of the posterior communicating artery (Figure 1, left). There also was a small (3 mm) aneurysm on the trunk of the left middle cerebral artery (Figure 1, right). The patient at first declined surgical operation, but later consented, and the right internal carotid

Figure 1.—(Case 1) In a 50-year-old woman, a right posterior communicating artery aneurysm (arrow, **left**) which had ruptured was noted on angiography. This lesion was successfully obliterated, but an aneurysm of the left middle cerebral artery (arrow, **right**) remains.

artery aneurysm was obliterated by an intracranial microsurgical approach 11 days after the subarachnoid hemorrhage.

The patient recovered without neurological deficit and returned to work. Over the four years since the procedure, the patient has continued to do well, though antihypertensive medication has been required for persistently elevated blood pressure. A mild seizure disorder may be present and diphenylhydantoin is being taken. So far, the patient has declined the recommendation that repeat angiography be done to rule out progressive enlargement of the left middle cerebral artery aneurysm.

Comment

When this patient presented to a hospital emergency room immediately following subarachnoid hemorrhage, a diagnosis of hypertensive headache was made because the blood pressure was elevated. However, elevation of the blood pressure is common following subarachnoid hemorrhage. Even if a patient has a history of hypertension, the development of headache cannot be ascribed with certainty to the hypertension alone, and the physician must keep in mind the increased incidence of subarachnoid hemorrhage in hypertensive patients.

It is not uncommon for subarachnoid hemorrhage to be misdiagnosed as some sort of abdominal disorder (see also Cases 3 and 5). The nausea and vomiting which frequently accompany subarachnoid hemorrhage may mask the importance of the headache, and the patient may have abdominal tenderness because of the persistent vomiting.

This patient is at considerable risk from the remaining left middle cerebral artery aneurysm and the hypertension increases this risk further. This author would recommend prophylactic microsurgical obliteration of the aneurysm if progressive enlargement was seen on serial angiography.

Case 2. A 41-year-old woman fell at home, striking her head on a television set. Further history, obtained subsequently, indicated that while watching television a severe headache developed. The patient arose from her chair, lost consciousness and then fell. This sequence of events was not recognized when the patient was seen in a hospital emergency room the morning following the event. Since ecchymosis was present around the left eye, it was assumed that the headache was the result of the head trauma. The patient was neurologically normal. It is not known whether or not nuchal rigidity was present at that time. The patient was observed in the emergency room for several hours, then released. However, the symptoms persisted, and an internist was seen two days later. The patient was admitted to hospital, at which time the blood pressure was 120/60 mm of mercury. The orbital ecchymosis was again noted. Results of funduscopic and neurological examinations were normal except for a suggestion of impaired graphesthesia in the left upper extremity. Nuchal rigidity was present.

Delayed venous drainage of the right cerebral hemisphere was noted on brain scan, though findings on blood brain barrier scintiphotos were normal. A lumbar puncture produced bloody cerebrospinal fluid with a pressure of 270 mm. The supernatant was moderately xanthochromic. On transfemoral cerebral angiography, an aneurysm of the right middle cerebral artery was seen. Craniotomy was carried out four days after the subarachnoid hemorrhage and the aneurysm was obliterated microsurgically. The patient did well postoperatively, though a minor seizure disorder subsequently developed and administration of anticonvulsants was required.

Comment

The subarachnoid hemorrhage caused the patient to lose consciousness and fall. The case was originally misinterpreted as one of straightforward cranial trauma. Since cranial trauma is a common cause of secondary subarachnoid hemorrhage, it may at times be difficult to distinguish between subarachnoid hemorrhage due to a ruptured aneurysm and that due to trauma. A careful history will help, but angiography may be necessary to investigate the possibility that a ruptured aneurysm led to the event responsible for the cranial trauma.

Case 3. A 55-year-old man was awakened from sleep one night by headache and severe neck pain. When admitted to hospital shortly thereafter, the patient was nauseated, vomited and had complaint of anterior chest pain and epigastric distress. A diagnosis of anterior myocardial infarction was considered. Peptic ulcer disease 12 years before the present illness had required gastric surgical operation, and recrudescence of this problem was also considered as a diagnostic possibility. Morphine was given and the patient soon

became lethargic to a degree out of proportion to the dose administered. Pronounced confusion was also noted, and the possibility of excessive self-medication at home was considered, as was the possibility of a psychotic reaction of some sort. Blood pressure was 120/60 mm of mercury. Findings on funduscopic and neurologic examinations were normal except for the lethargy and confusion.

It is not known if objective nuchal rigidity was present at the time of admission to hospital, but three days later an orthopedic consultant, called because of the patient's continuing neck pain, noted a stiff neck. A diagnosis of acute cervical strain was made, and the patient was placed in cervical traction.

Five days after admission neurological consultation was obtained and bloody cerebrospinal fluid with xanthochromic supernatant was found on lumbar puncture. Transfemoral cerebral angiography was carried out with the left vertebral and both carotid arteries being injected. The source of the subarachnoid hemorrhage could not be found, though in retrospect mild vasospasm was present in the left internal carotid artery (Figure 2, left). The lethargy and confusion resolved and the patient was discharged from the hospital 11 days following the subarachnoid hemorrhage.

One month after the initial hemorrhage, there was recurrence of severe headache and effective vision in the left eye was lost. Upon admission to hospital a large preretinal hemorrhage covering the left macula was noted. There were preretinal hemorrhages in the right fundus as well. Blood pressure was 110/70 mm of mercury, and nuchal rigidity was present. The patient was lethargic, but otherwise neurologically intact.

On lumbar puncture five days after the recurrence of the headache, xanthochromic cerebrospinal fluid was noted. A large anterior communicating artery aneurysm (Figure 2, right) was seen on cerebral angiography. The patient initially refused surgical operation, and 21 days following the recurrence of headache, still another sudden headache developed with nuchal rigidity. Lumbar puncture was not felt to be necessary. The patient agreed to surgical operation, and five days later craniotomy was carried out and the aneurysm obliterated with microsurgical techniques. A low-grade wound infection from the Providence group of Gram-negative organisms developed, but this responded well to gentamicin. The patient did well and returned to work. Vision in the left eye subsequently improved.

Comment

The presentation of the initial subarachnoid hemorrhage in this patient was confusing. Several diagnoses were initially considered, including anterior myocardial infarction, recrudescence of peptic ulcer disease, drug overdose, acute psychotic reaction and cervical strain.

The large anterior communicating artery aneurysm did not fill at the time of initial cerebral angiography, though in retrospect there was internal carotid arterial vasospasm which was a clue to the presence of the lesion. The aneurysm

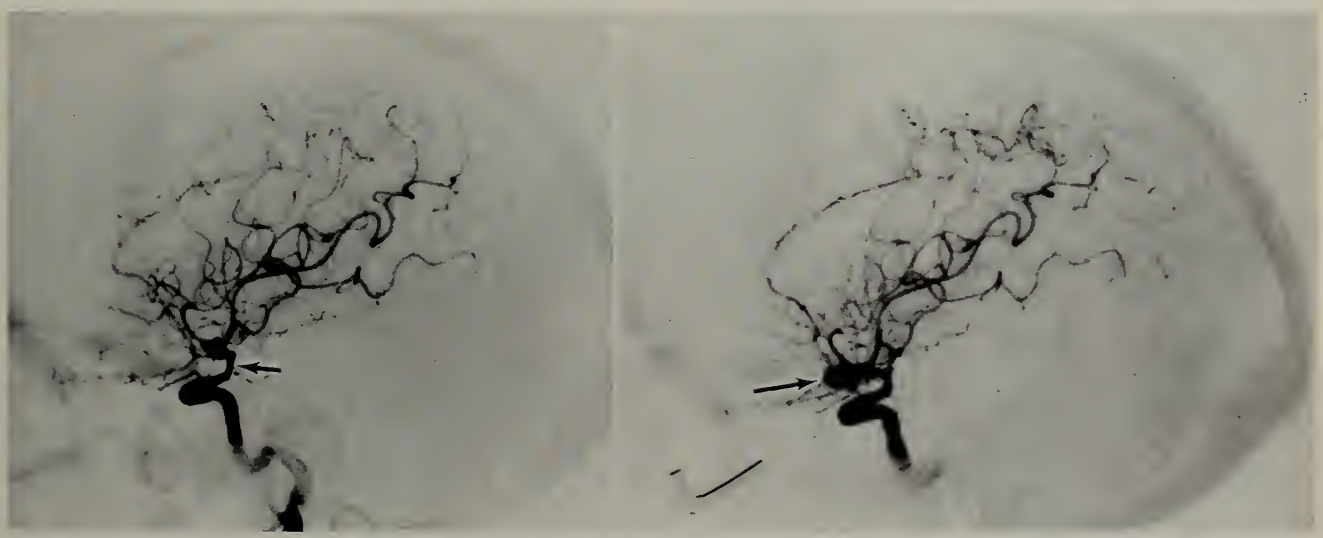


Figure 2.—(Case 3) In a 55-year-old man, a left cerebral angiogram (above, **left**) showed no aneurysm, though there was vasospasm of the left internal carotid artery (arrow). Left cerebral angiogram one month later (above, **right**) showed a large anterior communicating artery aneurysm (arrow).

filled well on a subsequent angiogram. This case well demonstrates the point that cerebral angiography should be repeated if the initial study does not show the source of an unexplained subarachnoid hemorrhage. The possibility that the source of the hemorrhage may be occult spinal pathology should be kept in mind. Intracranial subarachnoid hemorrhage can be mimicked by hemorrhage from a spinal cord vascular malformation, especially if the lesion lies in the cervical spinal cord. Intradural spinal tumors, particularly ependymomas, can also present initially with subarachnoid hemorrhage. If the source of the hemorrhage cannot be shown by cerebral angiography, then myelography and spinal angiography should be considered.

Case 4. In a 40-year-old woman, a stiff neck and occipital headache suddenly developed while she was playing tennis. An orthopedist, who was consulted, found no neurological abnormality. It is not known whether or not objective nuchal rigidity was present at that time. The headache persisted for two weeks, then subsided. One month later, again while she was playing tennis, severe headache developed and the patient temporarily lost consciousness. Upon admission to hospital, blood pressure was 140/80 mm of mercury. The patient was awake though confused, but shortly thereafter suddenly lost consciousness again and became apneic. After intubation, the patient regained consciousness but was combative. Right hemiparesis was present. The blood pressure then was 100/60 mm of mercury. On funduscopic examination, preretinal hemorrhages in the left eye were noted. Lumbar puncture was not done, since the diagnosis of subarachnoid hemorrhage seemed secure without it.

Two days after admission, a left infraclinoid carotid aneurysm (Figure 3) was noted on transfemoral cerebral angiography. The patient became fully awake and the right hemiparesis resolved, though there was some remaining confusion and a memory deficit. Five days after admission, a left frontotemporal craniotomy was carried out and the aneurysm successfully obliterated.

Following the craniotomy the patient was neurologically intact and mental status continued to improve until the fifth postoperative day when lethargy and aphasia with hemiparesis on the right developed. Cerebral angiography was repeated and severe spasm of the internal carotid, middle cerebral and anterior cerebral arteries was noted. Intravenously administered phenylephrine was used to increase the blood pressure. When the blood pressure dropped below 120 systolic, the patient became totally unresponsive and decerebrate posturing of all extremities developed. Gradually tolerance to the phenylephrine developed. Levarterenol was substituted, but the blood pressure become unresponsive to that medication as well.

On a third cerebral angiogram three days after

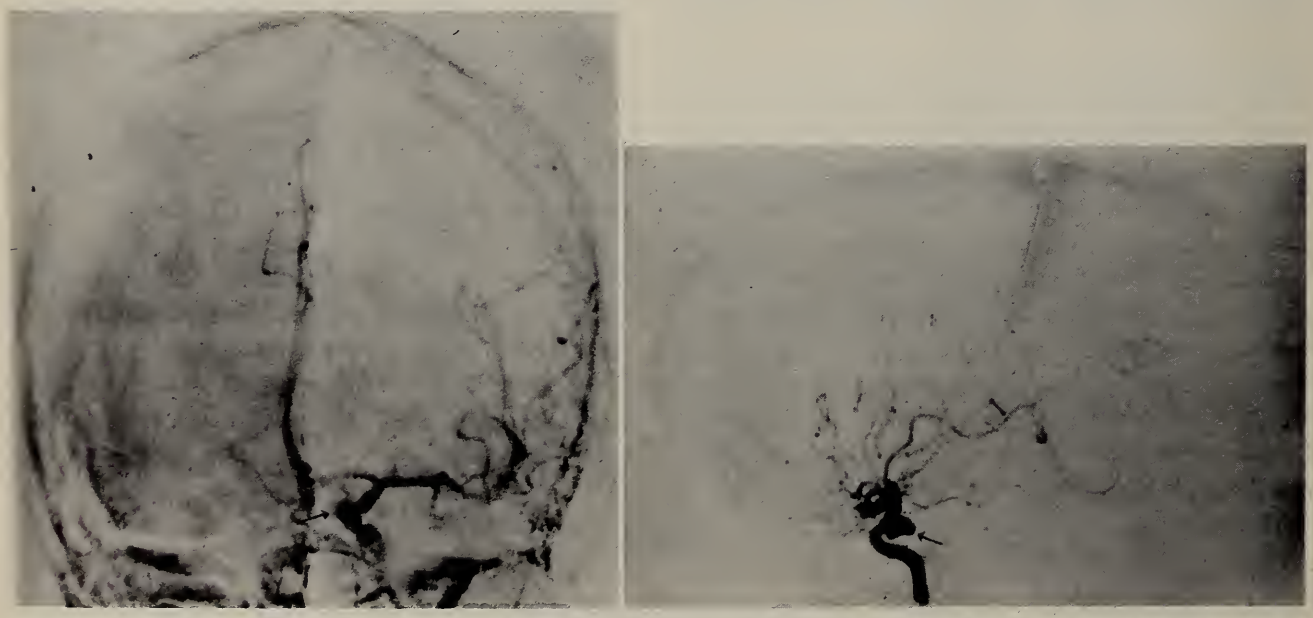


Figure 3.—(Case 4) In a 40-year-old woman, the infraclinoid internal carotid aneurysm (arrows) was clipped five days after the subarachnoid hemorrhage.

the onset of neurological deterioration, further increase in the spasm was noted. A left superficial temporal-middle cerebral artery microsurgical bypass was done, in the hope that this procedure would increase cerebral perfusion enough to reverse the deterioration. Immediately following the procedure the blood pressure was allowed to drift toward lower levels. Decerebrate posturing was no longer present. The next morning the vasopressors were discontinued, and the systolic blood pressure stabilized at 90. The neurological status began to improve, and 72 hours after the microvascular procedure the patient was fully responsive, was taking oral fluids and had returning function of the right arm. Neurological improvement continued, and at present—one year and a half after the episode—speech is normal and there is full use of all extremities. The patient is completely independent in the activities of daily living, but still lacks initiative and has some deficit in recent memory. As improvement continued, the superficial temporal arterial pulse gradually diminished, finally becoming imperceptible. On cerebral angiography two months after the microvascular procedure, it was noted that the microvascular bypass was no longer patent. Presumably it closed as normal cerebral circulation became reestablished.

Comment

In this patient, there almost certainly was minor subarachnoid hemorrhage one month before the major hemorrhagic episode—reflected by the sudden development of a stiff neck and occipital headache while playing tennis. Hemorrhage presenting in this form is extremely subtle and confusing, but the severity and persistence of the headache and the absence of a specific precipitating traumatic event might have been clues that the symptoms represented more than a simple cervical strain.

The major hemorrhage which precipitated admission to hospital almost resulted in immediate death. The patient did well immediately following the craniotomy, only to be placed at great risk again by the development of vasospasm associated with severe cerebral ischemia. The author feels that cerebral vasospasm in this patient represents the delayed phase of vasospasm which develops in approximately two thirds of patients following subarachnoid hemorrhage with or without intervening craniotomy.[9-12] (See also Case 5.) In humans, delayed vasospasm becomes maximal approximately one week following hemorrhage.[9] Delayed vasospasm is in some cases associated with severe cerebral ischemia leading to infarction,[13] and accounts for a number of the deaths resulting from subarachnoid hemorrhage. This type of vasospasm has proven resistant to direct treatment by any vasodilating drug now available, but if the ruptured aneurysm has been obliterated before the patient develops cerebral ischemia, then the ischemia can in some cases be reversed by the use of induced hypertension.[14,15] Induced hypertension presumably increases perfusion of the compromised cerebral tissue by taking advantage of the fact that circulatory autoregulation is impaired in the ischemic regions. Perfusion in these areas is directly proportional to the blood pressure. However, induced hypertension cannot be used safely if the patient still harbors a patent aneurysm, as Allcock and Drake have emphasized.[16]

The author has successfully used a regimen of induced hypertension in two other aneurysm patients severely threatened by cerebral ischemia which developed several days after craniotomy. In the patient reported above (Case 4), however, induced hypertension alone did not reverse the deterioration, and a microvascular shunt was carried out in an attempt to increase cerebral perfusion. It cannot be determined with certainty whether or not the microvascular bypass contributed to the patient's survival and neurological improvement, but the postoperative course suggests that it did.

Early diagnosis of a ruptured aneurysm and prompt obliteration of the aneurysm allow vigorous treatment of cerebral ischemia should it occur several days after the hemorrhage in association with delayed vasospasm.

Case 5. A 37-year-old woman awakened early one morning with a severe headache. Nausea, vomiting and diarrhea followed shortly, and the patient came to a hospital emergency room. She stated that she had eaten ham the day before, and in the past had had a "reaction" to this food. A history of recurrent headaches was given, and the patient reported a recent diagnosis of hypertension. Findings on neurological examination were normal, including results of funduscopic examination, though the presence or absence of nuchal rigidity was not recorded. Blood pressure ranged from 170/100 to 210/120 mm of mercury. Antiemetics and mild analgesics were given and the patient

was sent home with a diagnosis of acute gastroenteritis.

Four days later the patient was admitted to hospital after presenting to another physician with left hemiparesis and mild confusion. Blood pressure at that time was 160/108 mm of mercury. Results of funduscopic examination were normal and there was no nuchal rigidity.

On lumbar puncture, bloody cerebrospinal fluid with xanthochromic supernatant was noted. By the next day, lethargy and hemiplegia with a tendency toward decerebrate posturing on the left were present.

Findings on cerebral angiography indicated a large right internal carotid aneurysm, along with severe vasospasm of the internal carotid, middle cerebral and anterior cerebral arteries (Figure 4). At that point, the patient was not a candidate for surgical operation. Large doses of dexamethasone were given, but the patient continued to deteriorate and died 24 hours later.

Comment

This patient's case represents an extremely difficult problem in the management of subarachnoid hemorrhage. Cerebral vasospasm and progressive neurological deterioration following subarachnoid hemorrhage in a hypertensive patient is very frequently a lethal chain of events. Attempts to treat the hypertension by lowering the blood pressure may accentuate the cerebral ischemia. Attempts to increase cerebral perfusion by elevating the blood pressure are liable to cause massive hemorrhage from the aneurysm.

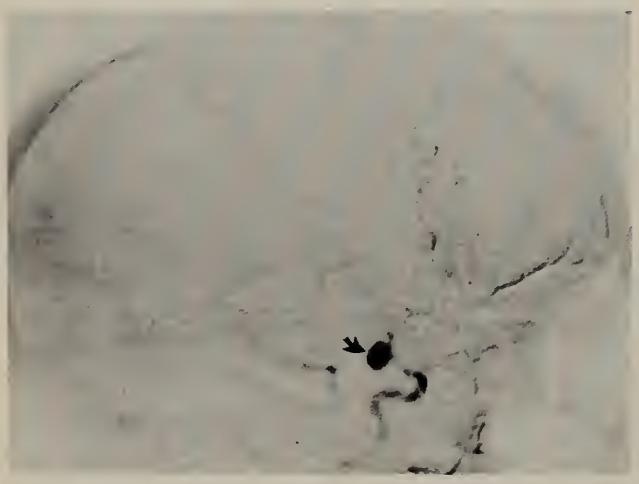


Figure 4.—(Case 5) Headache, nausea and vomiting in a 37-year-old woman was initially diagnosed as gastroenteritis. On angiography five days after onset of the symptoms, a large right internal carotid artery aneurysm (arrow) was seen. Severe vasospasm had developed by that time and no effective therapy was available. The patient died.

Diagnosis of the subarachnoid hemorrhage at the time of the patient's first presentation to the emergency room would have provided the only chance for survival. Obliteration of the aneurysm a day or two after the hemorrhage would have allowed treatment of the vasospasm when its effects became severe by attempting to increase cerebral perfusion either by further elevating the blood pressure with vasopressors or by carrying out a microsurgical vascular bypass.

Discussion

Pakarinen has shown that 32 percent of patients with ruptured intracranial aneurysms die within 24 hours of the major initial hemorrhage, and 35 percent die within three days.[17] However, in many patients before a major hemorrhage there are warning signs indicating expansion of the aneurysm or minor leakage from it.[8,18,19] Patients can be protected from the high initial mortality of a major hemorrhage if these warning signs are recognized and the aneurysm treated while the patient is still neurologically intact.

Okawara analyzed 112 patients with ruptured aneurysms and showed that in 48.2 percent there were warning signs before the major hemorrhage.[18] The incidence of warning signs in patients harboring internal carotid artery aneurysms at the origin of the posterior communicating artery was 69.2 percent. The average interval between the onset of warning signs indicating minor leakage of blood into the subarachnoid space and a major subarachnoid hemorrhage was 10.4 days.

Waga, Ohtsubo and Handa analyzed the clinical histories of 192 patients with intradural intracranial aneurysms.[19] In 49 percent of the 98 men and in 69.1 percent of the 94 women there were warning signs before a major hemorrhage. Warning signs occurred in 56.5 percent of patients with anterior cerebral aneurysms, in 48.8 percent of those with middle cerebral aneurysms and in 68.8 percent of those with intradural internal carotid aneurysms.

King and Saba found that in 106 (64 percent) of 165 patients with ruptured berry aneurysms, there were symptoms and signs forewarning a major subarachnoid hemorrhage, and a third of these patients had been treated for erroneously diagnosed illness for more than a week before subarachnoid hemorrhage was considered as a diagnostic possibility.[8]

In these studies, warning signs included sudden unusual headache, nausea and vomiting, transient loss of consciousness and transient visual disturbances. Expansion of an unruptured posterior communicating artery aneurysm can cause oculomotor nerve paralysis, resulting in various degrees of pupillary dilatation, ptosis and turning of the eye to the characteristic "down and out" position of third cranial nerve palsy.

TABLE 1.—*Misinterpretation of Signs and Symptoms in Subarachnoid Hemorrhage*

Headache
- Migraine
- Sinusitis
- Tension headache
- Hypertensive headache
- Subdural hematoma

Nuchal rigidity
- Cervical strain
- Ruptured cervical disc
- Meningitis

Nausea and vomiting
- Acute gastroenteritis or food poisoning
- Peptic ulcer disease
- Acute appendicitis (with tenderness of the abdominal wall)
- Anterior myocardial infarct (with epigastric or anterior thoracic discomfort)

Confusion, lethargy or personality change
- Drug overdose
- Alcoholic intoxication
- Acute psychosis

Hemiparesis or other focal neurological deficit
- Cerebral infarction from thrombosis or embolism
- Spontaneous intracerebral hemorrhage

TABLE 2.—*Initial Evaluation of Suspected Subarachnoid Hemorrhage*

History and general physical examination

Look for nuchal rigidity and elevated blood pressure.

Neurological examination

Look for signs of oculomotor nerve palsy, hemiparesis or other focal neurological signs.

Funduscopic examination

Look for retinal or preretinal hemorrhage.

X-ray studies of the skull

Look for intracranial calcification, an enlarged sella turcica, thinning of the dorsum sellae, or other signs of an intracranial mass lesion or elevated intracranial pressure.

Lumbar puncture

(Withhold lumbar puncture if retinal hemorrhages, papilledema or other signs of increased intracranial pressure are present.)

Look for blood or xanthochromia in the cerebrospinal fluid (CSF). A traumatic tap is distinguished by clearing of blood by the third tube and by the absence of xanthochromia in the centrifuged CSF.

Cerebral angiography

This should be done if subarachnoid hemorrhage is confirmed.

The initial symptoms in Case 4, above, fall into the category of warning signs. The initial symptoms in the other four patients reflect what this author would term major subarachnoid hemorrhage. As the case reports show, the symptoms and signs of subarachnoid hemorrhage can be misinterpreted in many ways (Table 1). The headache can suggest the presence of migraine, sinusitis, tension headaches, hypertensive headache (see Case 1) or subdural hematoma (see Case 2). The precipitous nature of the headache associated with subarachnoid hemorrhage is usually characteristic. Migraine usually has its onset before the age of 30 years and is not an isolated event. A single headache occurring suddenly in a middle-aged person is not very likely migraine. If there is any question concerning the diagnosis of migraine headache, a lumbar puncture should be done to rule out subarachnoid hemorrhage.

The nuchal rigidity of subarachnoid hemorrhage can suggest cervical strain (see Cases 3 and 4) or ruptured cervical disc. The sudden onset, the absence of a specific precipitating traumatic event and the usual association of the rigidity with occipital or generalized headache should make the examiner suspect that he is not dealing with a cervical syndrome. The precipitous onset should also differentiate the syndrome from meningitis, though a misdiagnosis of meningitis will at least lead to a lumbar puncture and the true nature of the disease process will be defined.

The nausea and vomiting associated with subarachnoid hemorrhage may mask the importance of the accompanying headache, and be misinterpeted as gastroenteritis (see Cases 1, 3 and 5). Prolonged vomiting may result in tenderness of the abdominal wall, thus leading to the diagnosis of an acute abdomen. If epigastric discomfort is prominent, occult anterior myocardial infarction may be considered (see Case 3).

Subarachnoid hemorrhage at times leads to lethargy, confusion or personality change misinterpreted as drug or alcoholic intoxication or as psychiatric disease (see Case 3). The absence of a history of drug overdose or alcoholic indiscretion along with the presence of a headache should help in narrowing the differential diagnosis.

Subarachnoid hemorrhage may be associated

with hemiparesis or other focal neurological deficit as the result of cerebral vasospasm or as the result of hemorrhage from the aneurysm into the cerebral substance or into the subdural space. Since both cerebral infarction from thrombosis or embolism and spontaneous intracerebral hemorrhage are often associated with blood in the subarachnoid space, angiography may at times be the only way in which to rule out a ruptured intracranial aneurysm as the cause of the patient's neurological compromise.

A patient in whom cranial, occipital or cervical pain has developed suddenly, especially if associated with stiff neck, syncope, confusion, personality change, hemiparesis, sensory changes, visual disturbances or seizures, should have careful neurological and funduscopic examinations, along with a lumbar puncture (Table 2). The lumbar puncture should be withheld in favor of angiography or computerized tomographic studies ("EMI" scanning) if the patient has retinal hemorrhages, papilledema or other signs of increased intracranial pressure. In all other patients in whom subarachnoid hemorrhage seems a diagnostic possibility, lumbar puncture should be done without hesitation. The indications for lumbar puncture and the techniques of the tap have been thoroughly reviewed recently.[20] The tap can be done in the office or emergency room with a No. 22 spinal needle. If there is no blood in the cerebrospinal fluid, and if there is no other evidence of a disorder requiring admission to hospital, the patient can be released after an hour or two of rest and observation.

If blood is present in the cerebrospinal fluid, a traumatic tap is usually distinguished by clearing of the fluid by the time the third tube is collected. The supernatant of the centrifuged specimen will usually, but not always, be xanthochromic if true subarachnoid hemorrhage is present.

If subarachnoid hemorrhage is confirmed, then cerebral angiography should be carried out promptly, preferably within 24 hours of the patient's admission, so that operative intervention or other appropriate therapy can be planned and instituted at the optimal time. If the patient is comatose or deteriorating, then angiography should be done as an emergency procedure to rule out an intracerebral or subdural hematoma possibly amenable to immediate evacuation.

Treatment of ruptured intracranial aneurysms by nothing more than bedrest and hopeful waiting is becoming passé. Whether an aneurysm is treated by microsurgical obliteration, antifibrinolytic therapy, stereotactic obliteration, a nonsurgical hypotensive regimen or endovascular obliteration by selective catheterization of the intracranial arteries, therapy must be planned and instituted as soon as possible—preferably before a major subarachnoid hemorrhage has occurred.

Our diagnostic goals should be prompt recognition of patients in whom there are symptoms and signs which reflect impending aneurysmal rupture and immediate recognition of patients in whom major subarachnoid hemorrhage has occurred. It appears that in a significant percentage of patients these goals are not being attained because subarachnoid hemorrhage is often an insidious process and may initially masquerade in many guises. The physician may be lulled into a false sense of diagnostic security until the patient deteriorates precipitously and passes beyond therapeutic reach.

REFERENCES

1. Yasargil MG, Fox JL: The microsurgical approach to intracranial aneurysms. Surg Neurol 3:7-14, 1975
2. Mullan S: Conservative management of the recently ruptured aneurysm. Surg Neurol 3:27-32, 1975
3. Nibbelink DW: The role of fluid restriction in treatment of acute subarachnoid hemorrhage following ruptured intracranial aneurysm (Abstract). Neurology 24:372-373, 1974
4. Slosberg PS: Treatment of ruptured intracranial aneurysms by induced hypotension. Mt Sinai J Med NY 40:82-90, 1973
5. Mullan S: Experiences with surgical thrombosis of intracranial berry aneurysms and carotid cavernous fistulas. J Neurosurg 41:657-670, 1974
6. Alksne JF, Rand RW: Current status of metallic thrombosis of intracranial aneurysms, *In* Krayenbühl H, Maspes PE, Sweet WH (Eds): Progr Neurol Surg, Vol 3, Basel, Karge; and Chicago, Year Book, 1969, pp 212-229
7. Serbinenko FA: Balloon catheterization and occlusion of major cerebral vessels. J Neurosurg 41:125-145, 1974
8. King RB, Saba MI: Forewarnings of major subarachnoid hemorrhage due to congenital berry aneurysm. NY State J Med 74:638-639, 1974
9. Bergvall U, Steiner L, Forster DMC: Early pattern of cerebral circulatory disturbances following subarachnoid hemorrhage. Neuroradiology 5:24-32, 1973
10. Brawley BW, Strandness Jr DE, Kelly WA: The biphasic response of cerebral vasospasm in experimental subarachnoid hemorrhage. J Neurosurg 28:1-8, 1968
11. Marshall Jr WH: Delayed arterial spasm following subarachnoid hemorrhage. Radiology 106:325-327, 1973
12. Wilkins RH, Alexander JA, Odom GL: Intracranial arterial spasm: A clinical analysis. J Neurosurg 29:121-134, 1968
13. Wilkins RH, Wilkinson RH, Odom GL: Abnormal brain scans in patients with cerebral arterial spasm. J Neurosurg 36: 133-140, 1972
14. Farhat SM, Schneider RC: Observations on the effect of systemic blood pressure on intracranial circulation in patients with cerebrovascular insufficiency. J Neurosurg 27:441-445, 1967
15. Wise G, Sutter R, Burkholder J: The treatment of brain ischemia with vasopressor drugs. Stroke 3:135-140, 1972
16. Allcock JM, Drake CG: Ruptured intracranial aneurysms—the role of arterial spasm. J Neurosurg 22:21-29, 1965
17. Pakarinen S: Incidence, aetiology, and prognosis of primary subarachnoid hemorrhage. Acta Neurol Scand 43 (Suppl 29):1-127, 1967
18. Okawara SH: Warning signs prior to rupture of an intracranial aneurysm. J Neurosurg 38:575-580, 1973
19. Waga S, Ohtsubo K, Handa H: Warning signs in intracranial aneurysms. Surg Neurol 3:15-20, 1975
20. Petito F, Plum F: The lumbar puncture. N Engl J Med 290:225-227, 1974

Refer to: Hine CH, Pasi A: Manganese intoxication. West J Med 123:101-107, Aug 1975

Manganese Intoxication

CHARLES H. HINE, MD, *and* AURELIO PASI, MD, *San Francisco*

We have reported two cases of chronic manganese poisoning. Case 1 followed exposure to manganese fumes in cutting and burning manganese steel. Case 2 resulted from exposure to dusts of manganese dioxide, an ingredient used in glazing of ceramics. There were initial difficulties in establishing the correct diagnosis. Prominent clinical features were severe and persistent chronic depressive psychosis (Case 1), transient acute brain syndrome (Case 2) and the presence of various extrapyramidal symptoms in both cases.

Manganese intoxication has not previously been reported as occurring in California. With increasing use of the metal, the disease should be considered in the differential diagnosis of neurologic and psychiatric disease.

Our observations were made in the period 1964 through 1968. Recently the prognosis of victims of manganese poisoning has been improved dramatically by the introduction of levodopa as a therapeutic agent.

MANGANESE IS FOUND in a large variety of minerals, sea and fresh water, marine and land plants, and animals. The ambient air concentration averages 0.1 microgram (μg) per cu mm.[1] Industrially, it is used principally in the manufacture of alloys, dry-cell batteries and chemicals. It is also found in glass, ceramics, paints, inks, dyes, matches, antiknock compounds, pigments, welding rods, drugs, rubber and wood preservatives, fungicides and fertilizers.[2] Manganese is an essential trace element, human requirements being estimated at between 3 and 9 mg per day. Small quantities are found in most human tissues; liver, pancreas, and bone contain the highest concentrations.

From the Division of Ambulatory and Community Medicine (Occupational Medicine Group) and Pharmacology (Toxicology Activity), School of Medicine, University of California, San Francisco.

Submitted, revised, May 14, 1975.

Reprint requests to: C. H. Hine, MD, PhD, P.O. Box 7604, Rincon Annex, San Francisco, CA 94120.

Manganese intoxication (manganism) is an uncommon disease affecting primarily the central nervous system and occurring mostly in chronic form. It is entirely occupational in origin and has never been reported from other sources. The greatest number of cases occur in the mining and processing of manganese ores.[2] Manganism has also been reported in ferromanganese metallurgy[3,4] in the preparation of manganese fertilizers and in the dry cell battery industry.[5] With the increased use of manganese in industry in recent times, increasing numbers of cases are appearing. Before 1966 more than 500 cases had been reported in the world literature.[6] The first report of manganese intoxication in the United States was that by Edsall and co-workers in 1919,[7] although Couper had reported in 1837 on the appearance of peculiar neurological features similar to Parkinson's syndrome in men grinding manganese oxide. Since no previous cases have been reported in

California, we are presenting two cases with the thought that these may help alert other practitioners to the diagnosis and treatment of this condition.

Reports of Cases

CASE 1.—For the past four years, a 27-year-old manganese steel welder had worked in a manganese steel foundry where his principal duty was to burn off metal projections from manganese steel castings. He had never been informed that there was any special problem connected with this operation and did not use any protective equipment. He was referred to the Occupational Medical Service at the University of California Hospital in July 1964 because of previous complaints of clumsiness in walking, lassitude, drowsiness, tremor in the extremities, recurrent spells of shaking, muscular weakness and cramps, speech disturbances, episodes of vertigo, depression and crying spells.

The patient's first indication of this illness was 18 months previously when he noted gradual onset of tiredness, lassitude and hypersomnolence; the latter symptom was so pronounced that he would fall asleep when he sat down to rest at his job. He had received medical treatment for depression and, following referral to a neurologist, a diagnosis of possible manganese intoxication had been made based on his occupational history of burning manganese steel and on laboratory reports of elevated concentrations of manganese in the urine (50 μg per liter). In May 1964 he had been treated with calcium disodium ethylenediamine tetraacetic acid (EDTA), 1 gram administered intravenously daily for six days and chlorpromazine (Thorazine®), 50 mg three times a day, with moderate subjective improvement over the following month. Except for spontaneous pneumothorax of the right lung in 1961 and minor traumatic fractures in 1962, the patient's medical history was unremarkable.

Clinical Findings

On physical examination, the patient's weight was found to be 78.3 kg (173 pounds) and his height was 178 cm (5 feet, 10 inches). Vital signs were normal. He was oriented as to place, person and time, but there was evidence of slowed thought processes. Responses to questioning were guarded, slow, halted, monotonic and frequently accompanied by a silly grin. Encouragement was necessary for the patient to complete his answers. His vocabulary was judged adequate for his education (9 grades) and cultural background. He conceptualized poorly on four proverbs. There were no delusions or hallucinations; the mood was depressed and he became tearful while discussing his feelings that he might not be able to maintain his hobbies, his family life and his job (in that order), and his general unworthiness. At rest, he presented a deadpan expression, flat affect and mild withdrawal. His station was characterized by a slumping position with the knees slightly bent, his gait was slow and guarded, but neither wide based or shuffling. He infrequently grimaced, but there were no other tics.

There was increased tone to the muscles of the neck, shoulder, girdle and the brachium, and normal tone of the lower extremities, but no true rigidity in any muscle group. There was no cog wheel movement elicited by a rapid passive stretching against resistance, but there was a sensation of stiffness to the muscles elicited by this maneuver. Deep reflexes were normal and no pathological reflexes were present. Mild nystagmus appeared on a lateral gaze. There was tremor of the extended tongue, closed eyelids and extended fingers. There was an inconstant spontaneous tremor which decreased on movements made to command. Observations were not recorded as to its disappearance during sleep. Neither slow nor rapid voluntary movements of the arms were impaired. The thoracic excursions were not impaired (4.6 cm increase on deep inspiration) and respiratory rate, depth and rhythm were normal. Examination of the cardiovascular system did not indicate any unusual findings. There was no organ enlargement, increased abdominal muscle tone or tenderness on palpation of the abdomen. Multiple scars were noted over the trunk and extremities, characteristic of the burns from hot metals experienced by welders. The remaining clinical findings were in the normal range.

Laboratory Data

Findings on hematogram, test of sedimentation rate and urinalysis were within normal limits. There was no deviation in the blood chemistry values recorded on the Sequential Multiple Analysis (SMA-12) panel; creatinine levels were normal, as were those for serum enzymes—lactic dehydrogenase (LDH) and serum glutamic oxalic transaminase (SGOT). A screen for hypnotic-sedative drugs and tranquilizers gave negative results on the second hospital day. The serum gamma

globulin was 7.2 mg per 100 ml (elevated). The finding on a Venereal Disease Research Laboratories test (VDRL) was negative. Examination of the spinal fluid indicated normal serology, cell count and glucose concentration, but an elevated protein of 66 mg per 100 ml. Analysis of metal content in the urine indicated normal values for lead, copper and zinc, but a slight increase in manganese to 16 micrograms (μg) per 100 ml. The manganese concentration in the blood was 3.6 μg per 100 ml. No abnormalities were seen on x-ray films of the chest and skull. Results of an electroencephalogram (EEG) showed a slight decrease of alpha activity in the left posterior temporal and occipital areas, a finding compatible with a slow potential focus. An electromyogram (EMG) and motor chronaxies, taken on both right and left anterior tibial, first dorsal interosseous and flexor digitorum sublimis gave normal findings. On a tremorgram, irregular slow tremor at two to three seconds in all extremities was noted. Results of Bender and Wait tests were not conclusive as to the presence of organic brain damage. Work evaluation tests indicated adequate work tolerance at low levels of effort, although shakiness followed tasks requiring repetitive, prolonged motion and there was clumsiness in fine work skills.

An industrial hygiene survey of the work area was requested and later we received data pertinent to the manganese concentration in various work locations of the plant. Air samples collected with an MSA electrostatic precipitator and analyzed by the persulfate method showed concentrations of manganese in the workroom air of 2.3 to 4.5 mg per cubic meter for welding operations without ventilation, 0.3 mg per cubic meter for floor burning and 11.5 mg per cubic meter in the aircair operation used at high temperatures. Analysis of the work practices indicated that the patient spent about two thirds of his time in the area with the highest air concentration of manganese, and though he wore a welder's hood, he did not wear a mask. There was no local ventilation and, because the cutting area was screened by heavy canvas, there was less than the desirable number of air changes per hour.

Clinical Course

The patient was seen on six occasions over the next two years. During the first 12 months, improvement was slow and incomplete. Trials in physical therapy with graded exercises were not well received because the patient disliked the interaction with other patients, but there was a gradual reduction of the increased muscle tone toward normal. Diazepam (5 mg three times a day) was given without effect on the depression and was discontinued after six months. The intention tremor was reduced following use of trihexyphenidyl hydrochloride (Artane®). Readings on EEGs had returned to normal on serial examinations by the end of 12 months. During the next 18 months, the concentration of manganese in the urine continued to be elevated on four occasions with concentrations varying from 100 to 150 μg per liter, while the concentration of the metal in the blood averaged only 2 μg per 100 ml.

There was a pronounced improvement at 18 months in the patient's overall mental and physical appearance, as well as a disappearance of the intention tremor and improvement in gait, posture, affect and thought processes. At 24 months, the patient had not fully recovered but was released for work. Reevaluation of his work site showed an improvement in general ventilation, but airborne manganese concentrations were still close to the threshold limit value; therefore, further exposures to the metal were advised against and the patient sought work as a mechanic with a different work group.

CASE 2.—A 57-year-old white man was admitted to Marin General Hospital in 1968 with an acute brain syndrome characterized by mental confusion, bizarre behavior, restlessness, increased agitation and ataxia. The patient remained confused for 48 hours, urinated on the floor, was restless and disoriented as to time and space. According to the history obtained three days later (when he became lucid), the illness had begun a week before with the onset of continuous coarse tremors, weakness in the legs, visual hallucinations and extreme malaise. The patient said that there had been no excessive alcohol intake, fever, change in excretory patterns, abdominal tenderness, dark urine or significant loss of weight. Despite symptoms, he had continued to work until the day of his break.

Clinical and Laboratory Findings

Further examination during the next two days identified continuing coarse intention tremor, dystonia of the legs with decreased muscle strength on extension, a dusky skin color, unsteady gait, positive Romberg's sign, positive Babinski's signs, a bilateral rotatory nystagmus, a withdrawn and

staring expression, an elevated blood pressure (180/90 mm of mercury) and a pulse rate of 96. There was enlargement of both liver and spleen to palpation. Findings on clinical laboratory tests —including a hematogram, urinalysis and tests of prothrombin time, electrolytes, blood urea nitrogen (BUN), fasting blood sugar, creatinine and isoenzymes (LDH and SGOT) were within normal limits. The sedimentation rate was 30 mm in the first hour (elevated). Manganese concentrations in urine varied, being 14 μg per liter at admission, 98 μg per liter one week later and 1 μg per liter at discharge after one month in hospital.

The patient returned to his employment. However, six weeks after the onset of his illness, he was referred to our occupational medical service because of continued complaints of weakness in the legs, increased susceptibility to fatigue and diminished ejaculation. Employment history obtained at that time indicated that he had worked for 25 years as a hard rock miner (working underground in tunneling and mining operations) and for the past 13 years as a general laborer in one of two ceramic plants. His job classification was that of clay mixer. As such, he had to prepare the mixes which went into glazes of ceramics and to add in the process powered manganese dioxide. This was done by dumping 50-pound sacks of the powdered material into a hopper. This operation was repeated four to six times per shift. He generally wore a dust mask during this operation, but did not wear one while sweeping up the contaminated working area. There was no draft hood over the mixer and the ventilation provided by two fans frequently caused an increase in airborne dust.

The medical history showed a severe fungus infection of the extremities during World War II, recurrent malarial attacks from 1943 to 1953, excessive smoking until 1964 and an increased alcoholic intake before 1966 during a year in which he was having family problems. A diagnosis of cirrhosis and ascites was made in 1966. The patient also experienced hypertension. No medications were being taken before the acute onset of illness or subsequent to release from Marin General Hospital—other than multiple vitamins.

On physical examination, a slight staring expression was noted, but no fixed appearance of the facies, and neurological findings were normal. Findings on an EEG consisted mostly of 9 per second alpha activity and there was a questionable slow wave focus in the left temporal-central region. There were no changes in thought processes. The patient seemed oriented, related his history in a normal fashion with good recall and showed no pathologic thought processes or unusual behavior. On repetitive raising and lowering of the weight on the balls of the feet for 20 times, the patient noted moderate discomfort in the calves. Appraisal of muscle strength indicated the muscle to be in good to fair grade. An EMG gave some evidence of lower motor neuron disease and conduction velocity studies showed borderline velocities in the arms (ulnar nerves). A minor right ventricular conduction defect was indicated on an electrocardiogram (EKG). Diffuse nodular densities in the lungs, indicative of pneumoconiosis, were seen on x-ray films of the chest. Results of further laboratory studies—including tests of LDH and serum protein electrophoresis and the chemistry values included in the SMA-12 panel—were within normal limits. A diagnostic Versenate® study involving 1 gram of calcium disodium EDTA in 500 ml of normal saline solution given by intravenous drip over one hour was carried out without significantly increasing the manganese excreted in the urine over the next 48 hours.

In manganism, differential diagnosis includes parkinsonism, hepatolenticular degeneration, disseminated sclerosis, myxedema, toxic drug responses and various psychoses. The most puzzling features are the presence of the plastic rigidity, slowness of movement, typical gait and tremor usually associated with parkinsonism. The differential diagnosis generally depends on finding a history of exposure to manganese fumes or powders and showing elevated manganese levels in the blood and urine.

In Case 1, the onset of the disease was slow and insidious. The condition was misinterpreted as "nervous depression" and treated with phenothiazine drugs. These by themselves can cause extrapyramidal symptoms. In this case, the symptoms were present before administration of the drugs, treatment was for only a month, dosage was low and there was no phenothiazine noted in the urine at the time the patient was admitted to hospital.

In Case 2, the patient had a history of alcoholism and there had been a previous diagnosis of cirrhosis and ascites. It was necessary to exclude acute brain syndrome from alcoholism or hepatic disease. The steady work performance of the patient before his break, the lack of odor of

alcohol on admission and the patient's statement that he had consumed no alcoholic beverages for six months were considered sufficient to distinguish this condition. The normal concentration of liver enzymes, normal bilirubin level, absence of ascites, liver tenderness, skin changes and the subsequent course of the disease were thought sufficient to rule out a liver crisis in the differential diagnosis. Due to the complaint of weakness, and since proper industrial hygiene control measures at the patient's place of employment had not been instituted, it was recommended that he discontinue his work for an additional period. He was assigned to a physiotherapy program for two months. By the end of that time, a hood had been installed over the mixer at his job, the general ventilation was improved in the area and a procedure for wet-mopping was substituted for sweeping. As the patient was then asymptomatic, he was permitted to return to work. Subsequent checks on the air concentration of manganese dust where he worked indicated that the threshold limit value (TLV) was not being exceeded.

Discussion

While the occurrence of manganism in ferromanganese metallurgy has already been reported, we could not find in the literature any evidence that this disease had previously been encountered among workers of the ceramic industry, nor had any cases been reported in California. Increased amounts of dust and fumes of the metal are important since industrial manganese poisoning occurs only after absorption from the respiratory system. The possibility of poisoning through ingestion of manganese as a contaminant of the hands is slight due to its low solubility. Since manganese in the inorganic form is not absorbed through the skin, the dermal route of exposure is not important. There is apparently no correlation between age, duration of exposure and onset of symptoms in industrial cases.

In the majority of cases reported, as well as in ours, poisoning appears after several years of exposure—although it may occur after as little as three months or as long as 20 years of exposure. The presenting signs and symptoms usually refer to the nervous system. Table 1 lists these. No correlation has been established between a history of alcoholism and the development of manganese poisoning.

In addition to the psychiatric and neurological disturbances characteristic of the chronic disease, one other form of industrial manganese poisoning occurs. This is an acute reaction of "metal fume fever" caused by inhalation of high concentrations of nascent manganese oxide, together with other metal oxides. Earlier reports (1921) indicated an association between high incidence of pneumonia and exposure to manganese. The majority of recent reports do not mention pulmonary disorders.[11] Animal experimentation confirms that no permanent pulmonary changes occur following exposure to manganese and there is no evidence of fibrosis. It is accepted that pulmonary infection may be complicated and aggravated by inhalation of manganese fumes.

The cause of the pneumoconiosis observed in Case 2 cannot be determined with any certainty because at one time the patient had worked as a gold miner. Various pulmonary complications have been observed in manganese miners with inconstant frequency, but their causes remain disputed.[4,11]

Interpretation of the clinical significance of the presence of elevated manganese levels in body fluids, feces and hair is difficult.[12] Normal manganese levels[13] are 2 to 8 μg per 100 ml for blood, 0.1 to 0.8 μg per 100 ml for urine and 0.4 to 1.2 μg per 100 ml for cerebrospinal fluid. Further, there is frequently a poor correlation between the severity of the acute disease and the quantity excreted in the urine. However, Horiuchi and coworkers[8] noted a parallel between the concentration of manganese in the air and proportionately elevated levels of manganese in the whole blood and the urine of workers. A significant correlation was also observed between the manganese content of the urine and neurological findings in workers in whom manganese intoxication was recent.

Smyth and associates,[14] in a study of workers in a ferromanganese plant, noted that in exposed workers manganese was excreted in urine at 7 to 10 μg per liter—about three times the amount excreted in unexposed workers. The average levels of manganese in the blood were the same for both groups.

In Case 1, although the blood levels assessed were normal, there was prolonged excretion of excessive amounts of manganese in the urine. In keeping with other reports,[2] this observation indicates the presence of deposits of the metal in the body. In miners with manganese poisoning, high concentrations of the metal have been found in lungs (the major point of entrance for airborne manganese) and in other organs, including the

brain. However, it has been shown that the presence of elevated tissue concentrations of the metal is not necessary for the continuation of the neurological symptoms.[8,9]

The attack rate for this disease is low in American workers. In contrast, Emara and associates[5] surveyed workers in the dry-battery industry who were exposed to dust containing 70 percent manganese oxide. They found that in 22.2 percent of the workers neuropsychiatric manifestations were present. In 16.6 percent, they noted chronic manganese psychosis. In only two cases were abnormal EEG changes seen. Dust concentrations in the main working areas, they indicated, ranged as high as 42.2 mg per cubic meter.

The therapeutic usefulness of chelation has not been settled. Administration of dimerceprol (BAL) has been tried without success by Goldman[19] on persons with chronic neurological deficit. Cook and co-workers[15] reported improvement with EDTA infusion in four of six patients. However, the improvement was found to be only temporary. It can be assumed, therefore, that metal chelation therapy will be ineffective in reversing chronic neurological manifestations, but its possible effectiveness in reversing psychiatric phases of chronic manganese poisoning remains to be investigated. A trial is justified on the observation that the manganese content of cerebral spinal fluid and urine is significantly elevated in persons showing recent manganese intoxication compared with the normal population or with asymptomatic workers at risk of exposure.

It is uncertain how manganese affects the brain to produce extrapyramidal symptoms.[16] Of significance was the demonstration of decreased striatal dopamine in Parkinsonians by Hornykiewicz in 1963 (cited in 17). Furthermore, the evidence summarized by Papavasiliou and co-workers[17] indicates that the same biochemical defect could well occur also in patients with chronic manganese poisoning. In fact, reversal or improvement of most of the neurological symptoms has been observed by the administration of L-dopa (an immediate biological precursor of dopamine), both in patients with Parkinson's syndrome and in victims of chronic manganese poisoning.[10] Unfortunately, this regimen had not been developed for manganism when we saw these patients.

Prognosis

In manganese poisoning with neurological symptoms, the evolution is frequently progressive, although some cases are stationary and others recover partially. Prognosis is more favorable in the young and those with only a few years of exposure. Complete recovery has been reported. Case 1 was characterized by slow and nearly complete remission. In this case at one year, some "parkinsonian" symptoms as well as chronic depression remained. Case 2 was of shorter duration, recovery being complete in nine months. Cases of persistent chronic psychosis from manganese intoxication have been reported by others.[5] Nystagmus, seldom reported,[9] was present in both our patients. Some minor and transient alterations on electroencephalogram, electromyogram and conduction velocity (CV) appeared in both patients. However, these changes seemed to bear no correlation to any of the neurological symptoms evident. Whereas the occurrence of EEG changes may be substantiated by other reports,[5] EMG and CV studies done by Nabi and co-workers[18] have conclusively shown that the peripheral nerves are spared by the intoxication. In our patients, as well as in the majority of reported cases, hematologic, cardiovascular and hepatorenal functions were not affected.

The diagnostic tests required to confirm a tentative diagnosis as manganism are: (1) the assessment of increased manganese levels in body fluids, (2) the positive EDTA response—that is, the in-

TABLE 1.—*Common Symptoms and Signs of Manganism*

Symptoms		
Psychomotor	*Neurologic*	*Signs*
Apathy	Clumsiness	Depression
Asthenia	Diplopia	Dysarthria
Compulsive acts	Muscle cramps	Expressionless facies
Emotional instability	Muscle weakness	Gait disturbance
Flight of ideas	Speech disturbances	Muscular hypertonia
Hallucinations	Stiffness	Pathologic laughter
Lassitude		Propulsion, retropulsion
Sleep disturbances		Tremors (upper extremities)

creased excretion of manganese in urine after administration of calcium disodium EDTA and (3) the reversal or improvement of the neurological manifestations after treatment with L-dopa.

Since there are no methods to predict individual susceptivity,[1] the emphasis of prophylactic efforts must be given to measures of personal and industrial hygiene and engineering control.[19] Biologic monitoring for the quantity of manganese in urine is recommended to determine the extent of the body burden. Physical examination of employees at work should be carried out with special emphasis on neurologic and psychiatric appraisal.

REFERENCES

1. Fishbein L: Natural non-nutrient substances in the food chain. Sci Total Environ 1:211-244, Nov 1972
2. Penalver R: Manganese poisoning, the 1954 Ramazzini Oration. Ind Med Surg 24:1, 1955
3. Whitlock CM Jr, Amuso SJ, Bittenbender JB: Chronic neurological disease in two manganese steel workers. Am Ind Hyg Assoc J 27:454, 1966
4. Balani SG, Umarji GM, Bellare RA, et al: Chronic manganese poisoning, a case report. J Postgrad Med 13:116, 1967
5. Emara AM, El-Ghawabi SH, Madkour OI, et al: Chronic manganese poisoning in the dry battery industry. Br J Ind Med 28: 78, 1971
6. Hassanein M, Ghaleb HA, Haroun EA, et al: Chronic manganism: Preliminary observations on glucose tolerance and serum proteins. Br J Ind Med 23:67, 1966
7. Edsall DL, Wilbur FP, Drinker CK: The occurrence, course and prevention of chronic manganese poisoning. J Ind Hyg 1:183, 1919
8. Cotzias GC, Horiuchi K, Fuenzalida S, et al: Chronic manganese poisoning. Neurology (Minneap) 18:376, 1968
9. Mena I, Marin O, Fuenzalida S, et al: Chronic manganese poisoning. N Engl J Med 282:5, 1967
10. Rosenstock HA, Simons DG, Meyer JS: Chronic manganism. JAMA 217:1354, 1971
11. Browning, Ethyl, M.D: Toxicity of Industrial Metals, 2nd Ed. New York, Appleton-Century-Crofts, 1969, pp 213-225
12. Horiuchi K, Horiguchi S, Shinagawa K, et al: On the significance of manganese contents in the whole blood and urine of manganese handlers. Osaka City Med J 16:29, 1970
13. Nilubol MLA, Chayawatanagkur K, Kritalugsana S: Manganese toxication in the human body determined by activation analysis. J Nucl Med 9:178, 1968
14. Smyth LT, Ruhf RC, Whitman NE, et al: Clinical manganism and exposure to manganese in the production and processing of ferro-manganese alloy. J Occup Med 15:101-109, Jan 1973
15. Cook DG, Fahn S, Brait KA: Chronic manganese intoxication. Arch Neurol 30:59-64, Jan 1974
16. Barbeau A: Rationale for the use of L-dopa in the torsion dystonias. Neurology (Minneap) 20:102, Nov 1970
17. Papavasiliou PS, Miller ST, Cotzias GC: Functional interactions between biogenic amines, 3′, 5′-cyclic AMP and manganese. Nature 220:74, 1968
18. Abdel Nabi SD, Kayed KS: EMG and conduction velocity studies in chronic manganese poisoning. Acta Neurol Scand 41: 159, 1965
19. Wynter JE: The prevention of manganese poisoning. Ind Med Surg 31:308, 1962

Medical
PROGRESS

Refer to: Stone RA: Dopamine-beta-hydroxylase—An index of adrenergic function in hypertensive patients (Medical Progress). West J Med 123:108-114, Aug 1975

Dopamine-Beta-Hydroxylase

An Index of Adrenergic Function in Hypertensive Patients

RICHARD A. STONE, MD, *San Diego*

Previous attempts to assess sympathetic nervous system activity in patients with hypertension have used a variety of physiologic, pharmacologic and biochemical techniques. Results have been conflicting and confusing. Recently, the activity in plasma of the catecholamine synthesizing enzyme, dopamine-beta-hydroxylase (DBH), has been proposed as an index of sympathetic nervous system activity. Studies of apparently healthy subjects show that high values (greater than 60 units per liter) for plasma DBH activity correlate with pronounced daily lability of blood pressure and frequent readings greater than 130/85 mm of mercury. Studies of patients referred for evaluation of established hypertension show significantly higher values for plasma DBH activity in patients with primary hypertension than in those with commonly recognized forms of secondary hypertension—that is, renovascular, renal parenchymal and adrenocortical. Therefore, the measurement of plasma DBH activity may be helpful in the study and differential diagnosis of hypertensive diseases. Measurement of DBH in plasma is inexpensive, reproducible and relatively easy to do.

ALTHOUGH THE ROLE of various etiologic factors that contribute to the development of systemic hypertension in man is not clearly defined, there is a voluminous literature that attests to the fact that the sympathetic nervous system contributes to the initiation or maintenance of one or more forms of hypertension.[1-6] Previous relevant observations have included the recognition of similarities between patients with pheochromocytoma tumors and those with primary (essential) hypertension, the description of experimental forms of hypertension in animals (which appear to be mediated by neurogenic factors)[3-6] and the established efficacy of sympatholytic drugs in the therapy of hypertension.[2]

Comparisons of catecholamine-mediated hemo-

From the Division of Nephrology, Department of Medicine, University of California, School of Medicine, La Jolla, and Veterans Administration Hospital, San Diego.

Some of the studies reported in this review were supported by grants from the Veterans Administration and the National Institutes of Health (HL 18095).

Reprint requests to: R. A. Stone, MD, Department of Medicine, Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, CA 92161.

dynamic responses in normotensive and hypertensive subjects before and after sympathetic blockade have suggested indirectly that activity of the sympathetic nervous system may be unusually intense in patients with hypertension, and the nature of such hemodynamic responses has been said to be predictive of the subsequent risk of hypertension and systemic vascular disease.[2,3] Hemodynamic investigations in patients with labile hypertension have described an elevated resting cardiac output, increased forearm blood flow and enhanced vasoconstrictor responses to verticle tilt.[6-8] Furthermore, some studies have shown accentuated hemodynamic responses to mental and physical stresses among patients with hypertension.[5,6] However, there are numerous studies which question an etiologic role for sympathetic nervous system activity in hypertension. For example, when the vasculature of persons with sustained essential (primary) hypertension is isolated from the nerve supply by the administration of sympatholytic drugs, the disproportionate blood pressure reduction (versus normotensive subjects) is often no different than that observed following the administration of hypotensive agents whose effects are mediated by non-neurogenic pathways.[2] In summary, despite strong indirect physiologic evidence that the sympathetic nervous system participates in the genesis of essential hypertension, it has been difficult to document relative differences between the degree of adrenergic function in normal and hypertensive subjects.

Catecholamine Measurements

Biochemical investigations of adrenergic activity in patients with primary hypertension also have yielded conflicting and confusing results. Most of these studies have attempted to contrast the urinary excretion of catecholamines or other metabolites in patients with hypertension to values observed in apparently healthy subjects with apparently normal blood pressures.[1] The results differ in many respects, but it may be significant to note that elevated urinary free catecholamine or metabolite excretions or both have been observed in some patients with primary hypertension. However, the potential importance of these observations has been lessened by the recognition of the fact that urinary catecholamine excretion may be influenced by factors other than sympathetic nervous system activity. More specifically, alterations of neuronal re-uptake and storage, tissue metabolism and renal handling may exert profound effects on urinary excretion of catecholamines. Thus, urinary catecholamine concentration may be helpful for the relative assessment of adrenergic function, but the influence of many additional factors suggests that other indexes must be used in order to gauge the activity of the sympathetic nervous system in patients with hypertension.

The measurement of plasma catecholamine concentration has been limited by the sensitivity and specificity of available methodology for many years. More recently, however, the development of a radioenzymatic assay for plasma catecholamine concentration has led to the discovery of the fact that the plasma concentration of norepinephrine may be increased in some patients with primary hypertension.[9-11] In fact, one group of investigators reported a very good correlation between plasma concentration of norepinephrine and diastolic blood pressure in patients with hypertension.[10] Furthermore, the same group observed a correlative reduction in both diastolic blood pressure and the plasma concentration of norepinephrine following the administration of a ganglionic blocking agent. On the other hand, as alluded to earlier, it again should be emphasized that the catecholamine concentration in plasma or urine may be influenced by many factors other than the degree of activity of the sympathetic nervous system. The possible contribution of local neuronal processes (re-uptake, storage, and so forth), endogenous metabolism and renal excretion may contribute importantly to the observed elevation of plasma catecholamine concentration in patients with primary hypertension.

Biosynthesis of Catecholamines

The biosynthesis of the neurotransmitter, norepinephrine, by a series of enzymatic steps is depicted in Figure 1. Tyrosine is transported across the neuronal plasma membrane and sequentially converted to dihydroxyphenalanine (DOPA), dopamine and finally norepinephrine (NE). The enzymes, tyrosine hydroxylase and amino acid decarboxylase are present in the cytoplasm of the neuron. The final step in sympathetic terminals is the conversion of dopamine to norepinephrine by the enzyme dopamine-beta-hydroxylase (DBH) inside the synaptic (storage) vesicle. In the adrenal medulla an additional transformation occurs, which is the synthesis of epinephrine from norepinephrine by the enzyme phenylethanolamine-N-methyltransferase.

Dopamine-Beta-Hydroxylase, The Theory

The most essential factor in providing supportive evidence of a basic neurogenic contribution to the pathogenesis of hypertension would appear to be the demonstration of increased *release* of norepinephrine into plasma. The measurement of plasma dopamine-beta-hydroxylase (DBH) activity appears to be better suited for this purpose than are assays of plasma norepinephrine concentration. As mentioned earlier, DBH is the catecholamine synthesizing enzyme that is released with norepinephrine in stoichiometric amounts from the synaptic vesicles of sympathetic nerve terminals, but there is no re-uptake, no known route of excretion and the biologic half-life appears to be much longer than that of norepinephrine.[12-15] The distribution and fate of DBH is illustrated in Figure 1. Results of animal experimentation show a decline of plasma DBH activity after chemical sympathectomy with 6-hydroxydopamine and an increase of enzymatic activity (along with blood pressure) after stress immobilization in rats.[16,17] Removal of both adrenal glands does not alter the effect of stress nor does it lower plasma DBH activity, suggesting that DBH in rat plasma is derived predominantly from sympathetic nerve terminals.[14] Therefore, the discovery of DBH in human blood led to the proposal that the activity of DBH in plasma may provide an index of sympathetic nervous system function in man.[18]

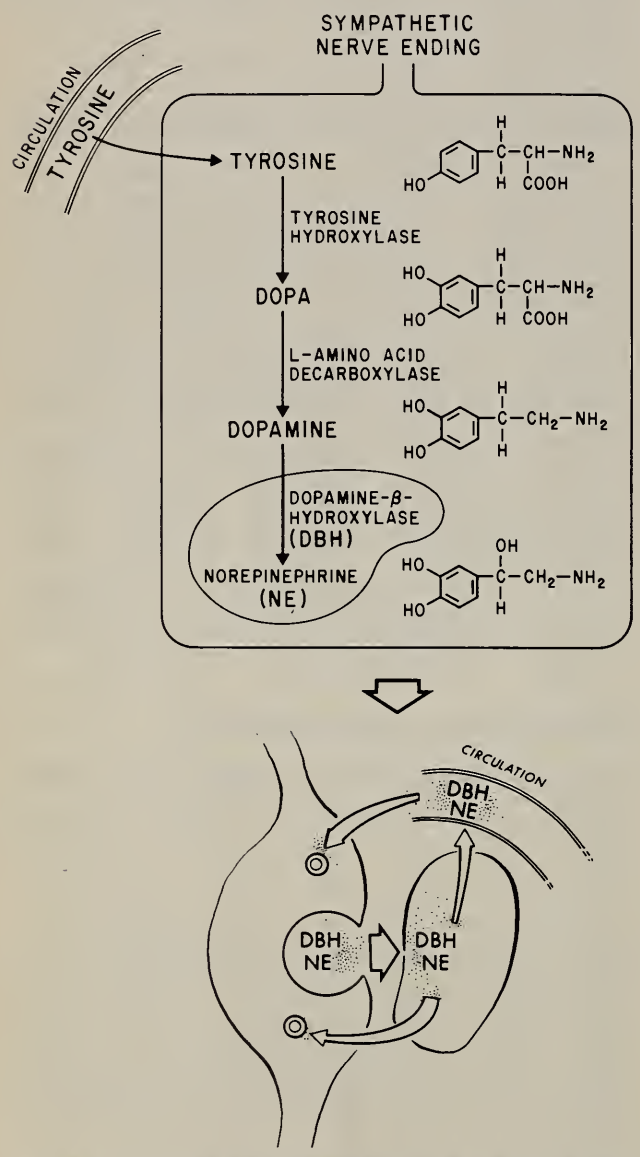


Figure 1.—Synthesis and release of norepinephrine (NE) in the sympathetic neuron. A neuronal impulse releases norepinphrine (NE) and the soluble portion of dopamine-beta-hydroxylase (DBH) into the synaptic cleft via exocytosis. The notably different fates of released NE and DBH are described in the text.

Many subsequent investigations have been carried out in humans and experimental animals in order to assess the accuracy of measurements of plasma DBH activity as an index of adrenergic function. Since many animal studies have used pharmocologic agents which may alter the amount of DBH in sympathetic terminals, or the mechanism of catecholamine release or both, the results are difficult to interpret.[19] Most studies in humans have assessed very acute physiologic alterations which are associated with changes of sympathetic nervous system activity. For example, investigators have measured the changes of plasma DBH activity that occur with the catecholamine-mediated acute hemodynamic alterations induced by the cold pressor test, Valsalva maneuver, vertical tilt and exercise. Since these experiments only attempt to measure short-term alterations of plasma DBH activity, the results have been conflicting.

Our own experiments suggest that any acute alterations of plasma DBH activity result from concomitant dilution or concentration of proteins in plasma.[22] Administration of a cold pressor test to healthy subjects was associated with an increase of plasma DBH activity (10 to 18 percent) in six of ten subjects. A parallel and similar directional change was observed in the activity or concentration of four other commonly measured plasma protein constituents (serum glutamic oxaloacetic transaminase, alkaline phosphatase, lactic dehydrogenase and total protein). In the two subjects in whom there was a diminution of plasma DBH activity, there was a parallel decline in large molecular weight plasma constituents. Alternatively, poor correlation was noted between changes of DBH activity and the concentrations of small molecular weight plasma components (that

is, blood urea nitrogen, serum creatinine and serum glucose). The high correlation between changes of DBH activity and those of higher molecular weight plasma components, versus a poor correlation with changes of smaller and more permeable plasma molecules support a proposal that acute alterations of DBH probably result from dilution or concentration of the enzyme in plasma.

Results of studies in humans over a more prolonged period are consistent with the ability of plasma DBH activity to reflect sympathetic nervous system function. One example of this relationship is shown in a study of plasma DBH activity versus 24-hour urinary catecholamine excretion.[23] The correlation between urinary norepinephrine concentration and DBH activity in plasma was excellent ($r = .90$). Thus, the possible physiologic and biochemical implications of short-term alterations of plasma DBH activity must be regarded as not yet established, and plasma DBH activity may reflect best adrenergic function over a more chronic time period. This hypothesis would be supported by the proposed long plasma half-life (hours to days) and the relatively large amount of DBH enzyme-protein in plasma versus the apparent small quantities in sympathetic terminals.

Immunoassay Versus Enzyme Assay

It also has been proposed that radioimmunoassay of DBH protein in plasma may more accurately reflect sympathetic nerve activity than the measurement of enzymatic activity in plasma.[24,25] However, studies using antisera prepared against human DBH have shown an excellent correlation between enzymatic and immunologic activity of the human enzyme.[26] The group that suggested a poor correlation between immunologic and enzymatic activity indicated that people may inactivate DBH at different rates.[24] However, the data from which their hypothesis was derived used heterologous bovine DBH as the antigen for preparation of antisera, and a study of the molecular properties of human DBH shows that several differences exist between human DBH and that of other species.[27] The different biochemical characteristics of the human enzyme might at least partially explain the observed poor immunologic cross-reactivity with antisera to DBH from animals and the weak correlation with enzyme assay of human sera. In conclusion, the activity of DBH in plasma (as measured by enzyme assay) appears to be a useful index of adrenergic function over a prolonged period. Measurement of immunologic activity also may be useful, but the antibody must be prepared to DBH from human sources.

TABLE 1.—*Plasma Dopamine-Beta-Hydroxylase (DBH) Activity in 100 Apparently Healthy Persons**

DBH (units/liter†)		*Subjects*	
Range	*Mean ± SEM‡*	*Number*	*Percent of Total*
Total Group			
2-100	31 ± 3	100	100
Subgroups			
2- 35	18 ± 1	78	78
36- 59	48 ± 2	8	8
over 60	78 ± 5	14	14

*Adapted with consent of editors from Circulation Research 34 and 35 (suppl I):47-56, 1974.
†International units (micromoles per minute) per liter of plasma at 37°C; micromoles octopamine formed.
‡Standard error of the mean.

Plasma DBH in Healthy Subjects

Measurements of plasma DBH activity in apparently healthy subjects (ages 22 to 35) are similar in all published investigations[23,28,29] and show a wide range of activity (2 to 100 units per liter). However, our own examination of the data suggested that a non-unimodal pattern of distribution exists.[23,28] In most subjects (78 of 100, or 78 percent), values were below 35 units per liter (average 18 ± 1 units per liter). On the other hand, in 14 of the remaining 22 subjects, values were over 60 units per liter (average 80 ± 5 units per liter) (Table 1). There was little day-to-day variation of DBH activity in each person. Additionally, systemic arterial blood pressure was stable and exhibited no more than modest variation in subjects with low plasma DBH activity (less than 35 units per liter). In distinct contrast, in persons with high plasma DBH activity (greater than 60 units per liter) there were very labile blood pressures from day to day, and blood pressure was greater than 130/85 mm of mercury on several occasions. Although the number of observations was small, results of these studies suggested that plasma DBH activity may be low and fall within a relatively narrow range in healthy young adults with stable, normal systemic arterial blood pressure. Alternatively, high DBH activity may represent incipient hypertension. Since Eich and co-workers[30] have suggested that labile hypertension may represent an early phase in the development of fixed essential hypertension, the aforementioned investigations suggest that plasma DBH activity may be useful for screening persons who are in the early phases of the disease.

DBH in Patients with Hypertension

Additional observations were made in 72 patients who were referred for the evaluation of hypertension.[29] These patients were extensively evaluated with numerous blood pressure determinations, plasma and urinary chemistry studies, and radiologic procedures. Using established clinical and laboratory criteria, these patients were assigned to one of six categories: (1) primary labile hypertension, (2) primary sustained hypertension, (3) primary hypertension with secondary renal abnormalities, (4) renovascular hypertension, (5) hypertension due to renal parenchymal disease and (6) adrenocortical hypertension.

The results showed several interesting facts (Table 2). In all patients with primary hypertension (the first three groups), there was high plasma DBH activity which differed significantly from the lower values in those patients with recognized forms of secondary hypertension—that is, those forms that were associated with renovascular, adrenocortical or primary renal parenchymal disease (Chart 1). Values for DBH activity were highest in patients with primary labile hypertension (mean: 71 ± 2 units per liter), and interestingly these higher values were similar to those in the aforementioned apparently healthy subjects with labile blood pressure. In addition, patients with labile hypertension were younger and the known duration of their abnormal blood pressure was of shorter duration than that observed in other groups (Table 2). Lower plasma DBH activity was observed consistently in patients with sustained primary hypertension and those with primary hypertension and secondary renal involvement (average: 55 ± 3 and 40 ± 2 units per liter, respectively), but these values were *consistently higher* than those observed in healthy subjects with stable blood pressure and in patients with secondary forms of hypertension. To the extent that multiple factors may be associated with the cause of primary or essential hypertension, there appears to be an increasing degree of overlap with secondary hypertension concomitant with the development of renal parenchymal abnormalities.

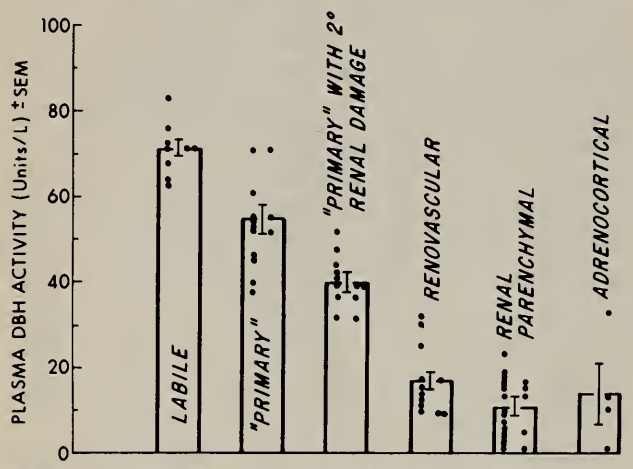


Chart 1.—The distribution of plasma DBH activity in 72 patients with hypertension. Vertical bars represent the mean and brackets represent standard error of the mean (SEM). (Adapted with editorial consent from Circulation Research 34 and 35 (suppl I):47-56, 1974)

TABLE 2.—*Characteristics of Hypertensive Patients*

Hypertensive Classification	*Average Age (yr) ± SEM*	*Average Duration High BP (yr) ± SEM*	*Average Plasma DBH (units/L) ± SEM*
1. Primary Labile	26 ± 1.3	1.3 ± 0.66	71 ± 2.0
2. Primary Sustained	40 ± 2.9	5.8 ± 1.0	55 ± 2.6
3. Primary with Secondary Renal Abnormalities	50 ± 1.6	19.0 ± 2.5	40 ± 1.7
4. Renovascular	51 ± 5.2	4.0 ± 0.9	17 ± 2.4
5. Renal Parenchymal	49 ± 2.4	5.6 ± 1.2	11 ± 1.5
6. Adrenocortical	48 ± 7.7	7.8 ± 2.4	14 ± 6.7

SEM = standard error of the mean
BP = blood pressure
DBH = dopamine-beta-hydroxylase

Conclusions

From a pathophysiological aspect, the above observations suggest that neurogenic factors contribute to the *initiation* of primary hypertension, at least in some patients. Additionally, the higher values for plasma DBH in healthy subjects with variable blood pressures and the parallel finding of similar values for DBH in patients classified as having primary labile hypertension suggest that the two groups may be similar. As alluded to earlier, it is possible that the patients with definite primary labile hypertension differ from apparently healthy subjects with high plasma DBH activity only in the degree or duration of blood pressure lability. The apparent inverse relationship between plasma DBH activity and age or duration of primary hypertension suggests that longer duration of hypertension and subsequent appearance of alterations of target organ function contribute to the maintenance of blood pressure elevation. It is not established what pathogenetic factors (for example, renal, hemodynamic, humoral) the target organs may contribute to sustained hypertension. However, it is of interest that the hypothesis of initiation of blood pressure elevation by one

factor (neurogenic) and maintenance of hypertension by other mechanisms has been proposed by others.[31,32] Our observation of the differences of plasma DBH activity among the three subgroups of primary hypertension are consistent with this proposal (Chart 1).

Unrelated to the pathogenetic implications of the above investigations are the possible clinical benefits that may be derived from the measurement of plasma DBH activity. The results suggest that plasma DBH activity may provide a valuable diagnostic tool in the evaluation of patients with hypertension. Such measurements may contribute importantly to the diagnosis of secondary forms of potentially curable hypertension where plasma DBH activity appears to be low. A low value for plasma DBH activity strongly suggests that hypertension may be secondary in character and that a search for causal factors should be instituted. However, it should be noted that the paucity of black patients and the absence of other non-white racial groups in the above studies indicates that these results may not be applicable to the non-white races. From a practical point of view, the assay is low in cost, easy to do and easily reproducible.

It should be mentioned that other studies of plasma DBH activity in primary hypertension have yielded conflicting results. The above results agree with the data of Wetterberg and co-workers,[33] who found elevated DBH in plasma in patients with essential hypertension, and with those of Geffen and co-workers,[34] who described good correlation between plasma DBH activity, diastolic blood pressure and plasma concentrations of norepinephrine. However, Horowitz and co-workers[21] reported no alterations of plasma DBH activity in patients with essential hypertension. The reasons for these different observations remain to be established, but several possibilities are apparent. The studies differ in the methodology of the assay procedures, the racial groups of the patients and the approaches used in the clinical classification of persons with hypertension. However, continued investigation (including a double blind trial with a clinic at another hospital) supports the usefulness of plasma DBH activity as a diagnostic aid in patients with hypertension.

In conclusion, our own studies have been concerned primarily with the use of DBH as an index of sympathetic nervous system activity in patients with primary hypertension. However, using plasma DBH activity as an index of adrenergic function, studies of patients with other disease entities associated with autonomic abnormalities have been made and have yielded interesting and provocative results. Results of one study have suggested a neurogenic contribution to the hypertension induced by oral contraception agents,[35] and results of other investigations suggest that the sympathetic nervous system may contribute importantly to the blood pressure abnormalities of patients with hemodialysis-induced hypotension.[36] Interestingly, the measurement of plasma DBH activity in children with Lesch-Nyhan syndrome has suggested a possible relationship between the hemodynamic response to neurotransmitter release and behavioral abnormalities.[37] Although all described investigations are dependent upon the precision with which plasma DBH activity represents adrenergic functions, studies in humans continue to accumulate suggesting that this is the situation.[38] It is anticipated that the measurement of DBH activity in plasma will provide important contributions to our understanding of sympathetic nervous system activity and, it is hoped, alter our diagnostic and therapeutic approach to human hypertension and to a variety of other pathologic states.

REFERENCES

1. Nestel PJ, Esler MD: Patterns of catechalomine excretion in urine in hypertension. Circ Res 26 & 27 (supp. II):75081, 1970
2. Windesheim JH, Roth GM, Hines EA: Direct arterial study of blood pressure response to cold of normotensive subjects and patients with essential hypertension before and during treatment with various antihypertensive drugs. Circulation 11:878-888, 1955
3. Doyle AE, Smirk FH: The neurogenic component in hypertension. Circulation 12:543-552, 1955
4. Finkielman S, Worcel M: Hemodynamic patterns in essential hypertension. Circulation 31:356, 1965
5. McKegney FP, Williams RB: Psychological aspects of hypertension: II The differential influence of interview variables on blood pressure. Am J Psychol 123:1539-1543, 1967
6. Frohlich ED, Kozul VJ, Tarazi RC, et al: Physiological comparison of labile and essential hypertension. Circ Res 27 (supp. I): 55, 1970
7. Conway J: Labile hypertension—The problem. Circ Res 27 (suppl. I):43, 1970
8. Esler MD, Nestel PJ: Sympathetic responsiveness to head-up tilt in essential hypertension. Clin Sci 44:213, 1973
9. Engleman K, Portnoy B, Sjoerdsma A: Plasma catecholamine concentrations in patients with hypertension. Circ Res 26 & 27 (suppl. I):141-146, 1970
10. Louis WJ, Doyle E, Anavekar S: Plasma norepinephrine levels in essential hypertension. N Engl J Med 288:599-601, 1973
11. Dequattro V, Chan S: Raised plasma-catecholamines in some patients with primary hypertension. Lancet 806-809, 1972
12. Viveros OH, Arqueros L, Kirshner N: Release of catecholamines and dopamine-B-oxidase from the adrenal medulla. Life Sci 7:609-618, 1968
13. Gewitz P, Kopin IJ: Release of dopamine-B-hydroxylase with norepinephrine during cat splenic nerve stimulation. Nature 227:406-407, 1970
14. Molinoff PB, Brimijoin S, Weinshilboum R, et al: Neurally mediated increase in dopamine-B-hydroxylase activity. Proc Natl Acad Sci 66:453-458, 1970
15. Depotter WP, Deschaepdryver AF, Moerman EJ, et al: Evidence for release of vesicle-proteins together with nor-adrenaline upon stimulation of the splenic nerve. J Physiol (London) 204:102-104, 1969
16. Lamprecht F, Williams RB, Kopin IJ: Serum dopamine-B-hydroxylase during development of immobilization-induced hypertension. Endocrinology 92:953-956, 1973
17. Williams RB, Lamprecht F, Kopin IJ: Serum dopamine-B-hydroxylase levels during development of hypertension in rats. J Clin Inves 51:104a, 1972

18. Weinshilboum R, Axelrod J: Serum dopamine-beta-hydroxylase activity. Circ Res 28:307-315, 1971

19. Reid JL, Kopin IJ: Significance of plasma dopamine-B-hydroxylase activity as an index of sympathetic neuronal function. Proc Nat Acad Sci 71:4392-4394, 1974

20. Wooten GF, Cardon PV: Plasma dopamine-B-hydroxylase activity. Arch Neurol 28:103-106, 1973

21. Horowitz D, Alexander RW, Lovenberg W, et al: Human serum dopamine-B-hydroxylase. Relationship to hypertension and sympathetic activity. Circ Res 28:594-599, 1973

22. Stone RA, Kirshner N, Gunnells JC, et al: Changes of plasma dopamine-B-hydroxylase activity and other plasma constituents during the cold pressor test. Life Sci 14:1797-1805, 1974

23. Schanberg SM, Stone RA, Kirshner N, et al: Plasma dopamine-B-hydroxylase: a possible aid in the study and evaluation of hypertension. Science 183:523-525, 1974

24. Rush RA, Thomas PE, Toshiharv N, et al: Comparison of human serum dopamine-B-hydroxylase levels by radioimmunoassay and enzymatic assay. Proc Nat Acad Sci 71:872-874, 1974

25. Rush RA, Geffen LB: Radioimmunoassay and clearance of circulating dopamine-B-hydroxylase. Circ Res 31:444-452, 1972

26. Ebstein RP, Park DH, Freedman LS: A radioimmunoassay of human circulatory dopamine-B-hydroxylase. Life Sci 13:769-774, 1973

27. Stone RA, Kirshner N, Reynolds J, et al: Purification and properties of dopamine-B-hydroxylase from human pheochromocytoma. Mol Pharm 10:1009-1015, 1974

28. Nagatsu T, Udenfriend S: Photometric assay of dopamine-B-hydroxylase activity in human blood. Clin Chem 18:980-982, 1972

29. Stone RA, Gunnells JC, Robinson RR, et al: Dopamine-beta-hydroxylase in primary and secondary hypertension. Circ Res 34 & 35 (suppl. 1):47-56, 1974

30. Eich RH, Cuddy RP, Smulyan H, et al: Hemodynamics in labile hypertension—a follow-up study. Circulation 34:299, 1966

31. Guyton AC, Coleman TG, Cowley AW, et al: Arterial pressure regulation. Am J Med 52:584-594, 1972

32. Tobian L: A viewpoint concerning the enigma of hypertension. Am J Med 52:595-609, 1972

33. Wetterberg L, Aberg H, Ross SB: Plasma dopamine-B-hydroxylase activity in hypertension and various neuropsychiatric disorders. Scand J Clin Lab Invest 30:283-289, 1972

34. Geffen LB, Rush RA, Louis WJ, et al: Plasma dopamine-B-hydroxylase and noradrenaline amounts in essential hypertension. Clin Sci 44:617-620, 1973

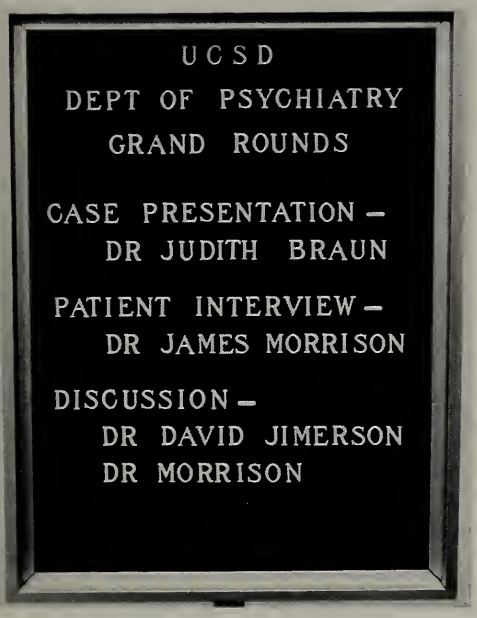
35. Rockson S, Stone RA, Gunnells JC, et al: Plasma dopamine-B-hydroxylase activity in oral contraceptive hypertension. Circulation 51:916-923, 1975

36. Lilley J, Golden J, Stone RA: Adrenergic function and hemodialysis hypotension (in preparation)

37. Rockson SG, Stone RA, Van der Weyden M, et al: Lesch-Nyhan syndrome: evidence for abnormal adrenergic function. Science 184:934-935, 1974

38. Naftchi NE, Wooten GF, Lowman E: Relationship between serum dopamine-B-hydroxylase activity, catecholamine metabolism, and hemodynamic changes during paroxysmal hypertension in quadriplegia. Circ Res 35:850-861, 1974

Refer to: Braun J, Jimerson D, Morrison J: Anxiety neurosis, depressive disorder and meprobamate addiction—Psychiatric Grand Rounds, University of California, San Diego, and San Diego Veterans Administration Hospital. West J Med 123:115-122, Aug 1975



Anxiety Neurosis, Depressive Disorder and Meprobamate Addiction

Based on Psychiatric Grand Rounds held at the San Diego Veterans Administration Hospital, a teaching facility of the School of Medicine, University of California, San Diego, in late 1973; edited by Barbara Blomgren, BA, and Leighton Huey, MD.

DR. BRAUN:* Janet Hull† was brought to the emergency room four months ago with complaints of fatigue, weakness and inability to do her housework for about six months. Mrs. Hull, who is 47 years old, has been married to the same man for 27 years, and they have eight children. Her husband is a contractor; she has trained herself to keep the company books, and together they have built a substantial business near Los Angeles. Although this was the first time she had been seen by a psychiatrist, Mrs. Hull had gone to other hospital emergency rooms complaining of palpitations, tingling and shortness of breath about ten times in the past 28 years and had been treated successfully with diazepam for what were called anxiety attacks.

Mrs. Hull had borne six children before she began thinking of limiting her family. When her fifth child was born by cesarean section she realized that she would need surgical operation for any future deliveries. Her seventh child was conceived while she was taking norethynodrel and mestanol. After that child was born she asked for a tubal ligation, but local hospital rules forbade it. Although her eighth child was initially unwanted, Mrs. Hull claims that as her pregnancy progressed she began to look forward to the birth. A boy was born healthy and without problems, and Mrs. Hull was granted a tubal ligation. At first she denied any sorrow about her sterilization, but recently she has spoken of the grief she felt. She did not want more children, but she missed the possibility of being able to be a mother again. She cared for her eighth baby without difficulty and apparently did not withdraw from him, but she says that her weakness and fatigue began around the time of his birth six years ago. She pushed on with her extensive household and accounting duties, arising each morning around two o'clock in order to accomplish everything. In addition to the six children still at home, she cared for her mother, who lives with her.

About four years ago Mrs. Hull began seeing her family physician about her fatigue and malaise. Findings on repeated physical and serological ex-

*Judith Braun, MD, Resident in Psychiatry.

†The patient's name is fictitious.

Reprint requests to: Barbara Blomgren, Editor, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA 92037.

aminations showed no organic source for her fatigue. She complained of difficulty getting to sleep at night and was given a prescription for meprobamate (Equanil®), which she claims helped her to get to sleep but did not affect her fatigue. She returned to her doctor many times during the four years.

About a year ago the family noticed a definite change in Mrs. Hull. She had more and more difficulty getting her housework and accounting done. She had to be coaxed to eat, and she lost 20 to 30 pounds the six months before admission to hospital. Her insomnia persisted; she continued to take meprobamate, claiming to take only three tablets a day. Her mother became ill with cancer of the cervix, and Mrs. Hull feels she did take good care of her mother during that illness despite her own fatigue. Her family says that Mrs. Hull was chronically pale and listless. She was often slightly ataxic in the morning and would return to bed. She denies being alarmed by her weakness, but her husband says that she was constantly worrying about dying and leaving him with all the responsibilities. She began worrying about their marriage and accused her husband of having affairs, which he emphatically denies. Both the Hulls claim that their sexual relationship has been undisturbed by her fatigue. Mrs. Hull's menstrual periods have continued to be regular. She has mentioned no suicidal thoughts and says that she has not had hallucinations.

She has not abused alcohol or drugs except for the chronic ingestion of meprobamate. About three weeks before admission she was stopped by the police for erratic driving and was ataxic when she got out of her car. The blood level of mepropamate was 4.2 mg per 100 ml. After that incident she was embarrassed and withdrew to her bed. Either her husband or her sister-in-law, who is a nurse, stayed with her day and night for two weeks. They are convinced that she took no medication at all during that time, and she had no ill effects from that apparent withdrawal of meprobamate.

Mrs. Hull was born in the Southwest, the second of two daughters. When she was about 12 years old her mother had an affair with an employee of her father. The sister eventually told the father about this, and the parents separated. A couple of years later, unable to tolerate living with their mother and her lover, the girls set out on their own, traveling, working and sometimes attending school. Mrs. Hull describes that period of her life as lonely and frightening. She completed high school, took some courses in business college and joined the Women's Army Corps for a time during World War II. She dated infrequently and decided to marry her husband after knowing him for only 19 days. She has had no other sexual relationships.

Shortly after their marriage, Mrs. Hull's sister died of a pulmonary embolism secondary to a cesarean section. Mrs. Hull grieved deeply and often thinks of her sister on the anniversary of her death. Although she had considerable anger toward her mother, Mrs. Hull felt that she ought to take care of her, and her mother came to live with her more than ten years ago. The mother is described by the family as a morbid person, and Mrs. Hull says she is very cold and aloof; she does not remember her mother kissing her, even in childhood.

When Mrs. Hull was admitted to the hospital she was emaciated and looked far older than 47. Lying in bed, she responded appropriately to questions and became tearful as she was discussing how much she *should* do and how much she was *unable* to do. During the physical examination she kept her arms around my waist, not wanting to let go. She was oriented to place and person, but not to time. She changed her history several times, and she refused to do calculations. She forgot details of a story I told her, but she was able to recite five digits forward and four digits backward without error. I found no evidence of a formal thought disorder. She was very concerned about abandonment and death. She was afraid that if she went to sleep she would not wake in the morning. Her fear of her husband having affairs was the only evidence of delusional thinking. She had a fairly normal range of affect, with depressive qualities. Although she used a great deal of denial, she did recognize that she was ill in some way.

Findings on the physical examination were normal except for her refusal to stand for fear of falling. Results of pelvic, rectal and neurological examinations were normal. Laboratory studies—including lumbar puncture, brain scan, Papanicolaou smear and complete blood chemistry—showed no organic cause for the illness. Neurological and medical consultants also could find no evidence of organic disease.

Mrs. Hull was disoriented and confused at times during her first few days in hospital. When I learned from her husband that she had taken five

tablets of meprobamate immediately before coming to the hospital, I prescribed meprobamate (800 mg every day for five days and then 400 mg every day for five more days), taking into account that complete withdrawal had apparently been accomplished at home two weeks earlier without bad effects. Mrs. Hull integrated herself into our therapeutic community fairly rapidly. She was not tearful or afraid. On her sixth hospital day she had one major motor seizure and another that may have been a major motor seizure. The blood chemistry at that time was entirely normal. Findings on an electroencephalogram (EEG) the following day were indeterminant, and a tracing three days later showed a dysrhythmia Grade II. Neurologists felt that this represented an intrinsic focus, and was not the result of either drug ingestion or withdrawal. Because I interpreted her seizures as meprobamate withdrawal seizures I reinstituted the higher dose of the drug and, on the recommendation of neurologists, also prescribed phenobarbital and diphenylhydantoin.

After the seizures Mrs. Hull's behavior changed dramatically, becoming slightly hypomanic—with pressured speech, inability to sit still, extreme busyness and inability to listen. She became afaid that she would be sexually assaulted on the ward. One week after her seizures she discussed her sexual fears in a group therapy session. The possibility was raised that perhaps she was having sexual fantasies about the men on the ward; she denied this emphatically.

The following day a telegram arrived saying that her daughter was critically ill and that she should return home immediately. She showed the telegram to several people and departed the next day without telling anyone she was leaving. (She later told me that she sent the telegram to herself.) The family called me several hours later, and I encouraged them to bring her back. With much agitation and a show of force they managed to transport her back here.

On return she was given thioridazine (100 mg every day), and within a few days her behavior became much less agitated and more appropriate. She was less sexually preoccupied. She was concerned about the seizures and her addiction, and made several unsolicited promises to me never to take meprobamate again. Remaining another two weeks for withdrawal from meprobamate, she participated appropriately on the ward, although she would not take any psychological tests. At the time of discharge her affect had a full range, but she was still using denial about her home life and problems in her marriage.

I have continued to see Mrs. Hull for an hour every other week. We have dealt with her concept and expectations of herself. She is an industrious and intelligent woman. She agreed to get some help in her house and to satisfy some of her own needs. She discussed at length her feelings of obligation to her mother, toward whom she feels much anger. She felt left out of the business and the household because of her reduced responsibilities when she returned home from the hospital. She also felt that her husband did not like her to be assertive and was thinking of leaving her. In a joint session, it became clear that Mr. Hull was indeed threatened by his wife's assertiveness, but he denied having an affair and reaffirmed his love for her. They agreed that Mrs. Hull would become partially reinvolved in the business to increase her sense of belonging, and they promised to try to communicate more directly with one another.

Concerned about a recurrence of the depression that Mrs. Hull's meprobamate addiction and subsequent hypomania had masked, a month ago I prescribed amitriptyline hydrochloride (150 mg every day), and she has improved considerably. She is scheduled to have an EEG done within the next month, and on the neurologist's recommendation I have continued the diphenylhydantoin until then. Mrs. Hull is beginning to pull away from therapy, mentioning the six-hour round trip drive here every other week as a burden, and after the interview I would appreciate discussing where to go from here.

(The patient was escorted into the room and introduced to Dr. Morrison. The following was excerpted from their interview.)

DR. MORRISON:* Mrs. Hull, thank you for coming in and talking in front of this rather large group of people this morning.

Patient: Well, I'm glad to come.

DR. MORRISON: Good. Can you tell us a little about what brought you to the hospital several months ago?

Patient: Well, I guess I should start about six months prior to when I came to the hospital. That seemed to be the point that it all came to. Of course I had been taking Equanil through the doctor's prescription for seven years. I told the doctor that I didn't feel like it was doing me

*James Morrison, MD, Assistant Adjunct Professor of Psychiatry.

any good, and I just couldn't pinpoint why I wasn't feeling better, you know. The last six months I just seemed to drop down lower and lower. Of course I had lost a lot of weight. I have gained back quite a lot now, but I carried about 90 pounds when I was home. I was real thin . . . and real nervous.

DR. MORRISON: You had been taking Equanil for seven years. Why?

Patient: Well, it wasn't excessive really. I had trouble through a pregnancy that required I stay in bed for about 10 or 12 weeks. My doctor gave me the medicine to keep me from being so jittery, I guess, just lying in bed all day long, you know. And of course I had to go to the hospital three or four times in that period, and then after I had the cesarean he said to still take this, and that carried on from him to this other doctor. And of course I had stated to the doctor that I was quite nervous.

DR. MORRISON: In years gone by had you suffered from attacks of nervousness?

Patient: No, not really. I don't think any more than anyone else. Of course things sometimes would make me upset. You know, if I thought someone was ill—those sorts of things.

DR. MORRISON: I got the impression from Dr. Braun that every year or two you had had an attack of feeling nervous, when you had trouble breathing and had to go to the emergency room or to the doctor to get a shot.

Patient: Well, she did state that right, although it was mostly over the last five or six years that I'd come to the point that someone called the fire department for a resuscitator. Even that didn't seem to help; on two occasions I was sent to the hospital.

DR. MORRISON: I see.

Patient: But many, many times I was just lying there with my husband or someone looking out for me because I was breathing so fast. It was something I had no control over.

DR. MORRISON: You must have felt very weak at those times.

Patient: Yes. I just couldn't sit up.

DR. MORRISON: What would be your state of mind at a time like that?

Patient: Well, it wasn't that bad; I just was hoping that it would stop.

DR. MORRISON: Would you be fearful?

Patient: I guess I was the last two times, going to the hospital.

DR. MORRISON: Would you ever be afraid that you were about to die, for instance?

Patient: Oh, yes. It came to the point when the breathing was so bad that I didn't feel I could gather another breath.

DR. MORRISON: Would you get chest pain at those times?

Patient: No.

DR. MORRISON: Or did you ever notice that your heart seemed to skip beats or beat very fast?

Patient: Oh, yes. That was what it was doing.

DR. MORRISON: Would you perspire excessively at those times?

Patient: Um hum.

DR. MORRISON: And would you notice any numbness or tingling in your hands or feet or around your lips?

Patient: No, I don't remember that.

DR. MORRISON: When was the first time you had an attack like that?

Patient: Well, I would put it back 20 years. But it was never a thing that you concentrated on, you know. It was just something that would happen on occasion.

DR. MORRISON: How long would the attacks last?

Patient: If they were bad they would last maybe 12 hours.

DR. MORRISON: Did you have to stop your normal activities and just lie there and suffer, or what?

Patient: Well, when I had it at home I didn't go to the doctor; I'd just lie there till it stopped.

DR. MORRISON: Now, since your last child was born, do I understand correctly that you've had an increase in these attacks?

Patient: I guess so.

DR. MORRISON: Has a doctor ever told you that you have any kind of lung or heart disorder? Has anything physical been found to explain your attacks?

Patient: No. I have had rheumatic fever. My old doctor seemed to think it could come from the rheumatic fever, but he didn't say that it did.

DR. MORRISON: And in the last year, how often were you having these anxiety attacks?

Patient: Maybe once a week. It's hard to say.

DR. MORRISON: Would they last 12 hours or so?

Patient: Oh, no. Not always.

DR. MORRISON: I wonder if you might tell us how your spirits were during the six months before you entered the hospital.

Patient: I guess they were all right, except I did get depressed because I was feeling bad.

DR. MORRISON: Feeling bad in terms of being listless or tired?

Patient: Um hum. Or maybe disgusted.

DR. MORRISON: Did you ever feel so disgusted that you felt there was no use going on?

Patient: Oh, no. Never.

DR. MORRISON: Did you have crying spells?

Patient: Well, yes. It wouldn't be just because I was feeling blue. There were not too many. I mean, to be perfectly frank, it would be when the children were causing me a litle trouble or when my husband and I had a little rough time. That always upset me a lot.

DR. MORRISON: Do you think you were crying more in those last six months?

Patient: Um hum.

DR. MORRISON: I understand your appetite suffered to some extent. How long had it been poor?

Patient: For maybe ten years.

DR. MORRISON: And how long ago was it that you began to lose weight?

Patient: Well, that was more of a gradual thing. I guess after the last boy was born I lost down to about a hundred pounds or so.

MR. MORRISON: What sort of trouble were you having with your sleep?

Patient: Well, I dreamt a lot and woke up very often also. I was getting up very early—two or three o'clock in the morning.

DR. MORRISON: What did you do when you got up? Would you have lots of energy and get things done?

Patient: I really did. It was surprising.

DR. MORRISON: So your energy wasn't failing you?

Patient: No, it didn't seem to. In fact, you know I kept the books for my husband, and that's usually when I worked on them, in the morning. In fact I sort of enjoyed it.

DR. MORRISON: So you kept your interest in things pretty well up until—when?

Patient: I guess about 20 days before I came here.

DR. MORRISON: As I understand it, though, there was a difference for you of some kind last winter, when you took to your bed? Can you tell us something about that?

Patient: I guess it was around January that I started losing interest in the home—I never did in the children and my husband—just in the home and cooking. I just used to take off to bed as soon as supper was finished and go to sleep. I was just exhausted.

DR. MORRISON: And did you notice any change in your spirits at that time?

Patient: Yes, they were down.

DR. MORRISON: Were there times that you felt pretty good?

Patient: Well, like I said, early in the morning I really felt like doing something. But then these other times I really was pushing myself.

DR. MORRISON: Well, how are you feeling now? Are your spirits up to about where they ought to be?

Patient: I would say so, and my husband thinks so. He said in fact I'm getting kinda ornery.

DR. MORRISON: What does that mean?

Patient: He means that I can hold my own with him. He's a little stubborn.

DR. MORRISON: I see. So you're back in fighting form.

Patient: You have to be with him. I think he kinda overtook me there for a while, you know.

DR. MORRISON: Well, thank you again for coming in and subjecting yourself to this.

Patient: Well, that's all right. I mean I just told you everything I know to the best of my ability.

DR. MORRISON: You were very helpful.

Patient: Well, thank you.

(The patient was escorted from the room.)

DR. MORRISON: Apprehension and psychic tension occur in virtually all psychiatric conditions,[1] and therein lies a problem; anxiety can be both a symptom of illness and a syndrome. We refer to a syndrome of anxiety attacks as *anxiety neurosis* when the attacks are not associated with other psychiatric conditions or with physical conditions like heart or lung disease, or with fear-invoking situations. This venerable syndome has been known for at least 75 years and goes by a number of other names, including neurasthenia, neurocirculatory esthenia, effort syndrome, soldier's heart, and perhaps 15 more. In their classic study of anxiety neurosis, Cohen and White[2] estimate that the condition may be seen in as many as 5

percent of the general population, and that perhaps 10 percent of patients seen in a cardiologist's office suffer not from organic heart disease but from anxiety neurosis. In a recent study of psychiatric outpatients by Woodruff and co-workers[3] in St. Louis, 12 percent of 500 patients interviewed were diagnosed as having anxiety neurosis.

The mean age of onset is in the early twenties, and the diagnosis is untenable if the onset occurs past the age of forty. Twice as many women as men suffer from anxiety neurosis. The anxiety tends to come in discrete attacks, not necessarily precipitated by fear-invoking situations. The person feels that something terrible is about to happen, that she is about to die. A sine qua non of anxiety neurosis is shortness of breath, either difficulty in catching one's breath or rapid breathing such as Mrs. Hull reported. The attacks are often immobilizing. The patient may have to sit or lie down and be afraid to move a muscle. Other symptoms include palpitations of the heart, tremors, paresthesias, numbness or tingling in the extremities or around the mouth, and pronounced weakness. Depressive thoughts or symptoms of depression probably occur in five out of six of these patients.[4] In Woodruff's[3] experience half the patients with anxiety neurosis suffered from a secondary affective disorder.

The origin of the condition is not clear. Perhaps 15 percent of parents and siblings of patients with anxiety neurosis also suffer from it. Slater[5] found about 50 percent of monozygotic cotwins of probands with anxiety neurosis also received that diagnosis, whereas only about 4 percent of dyzygotic cotwins of probands were so affected. Moreover, in a study of separately reared monozygotic twins there was essentially no difference in the interclass correlation coefficients on a test of neuroticism, indicating that environment cannot be presumed to be the differentiating factor. There appears to be some genetic factor in the predisposition to neurotic symptoms in general and to anxiety neurosis in particular.

The course of anxiety neurosis is chronic and benign. On 20-year follow-up most patients still have some symptoms, but well over half of them experience little difficulty. Perhaps a quarter of patients on long-term follow-up have occasional difficulty participating in normal activities, but they usually work around this by altering their lives in subtle ways. Perhaps 15 percent of patients have severe symptoms and disabilities, and it remains to the physician to decide upon a course of action to help these people.

Dr. Jimerson:* In this case it might also be helpful to take a closer look at the drug of abuse. The synthesis of meprobamate was part of an effort about 20 years ago to develop less toxic drugs to replace the barbiturates in the treatment of tense and anxious psychoneurotic patients. Early animal studies suggested that meprobamate possessed, in addition to anticonvulsant and interneuronal blocking capabilities, a unique tranquilizing property that made treated animals tame and docile without sedation or autonomic or extrapyramidal side effects, and without interference with intellectual or motor performance.

Meprobamate was first introduced in 1955, and effective advertising campaigns supplemented the early clinical reports of almost magical reduction of anxiety. That first year sales totaled nearly 2 million dollars.[6] For some years, case reports and studies of uncritical design continued to present meprobamate as panacea. By 1962, however, Weatherall[7] noted that 80 to 90 percent of the reports were "unacceptable" research.

The three important clinical effects of meprobamate are psychophysiological reduction of anxiety, prevention of petit mal seizures (for which it is less effective than trimethadione—in fact, meprobamate may aggravate grand mal epilepsy or myoclonic seizures) and relaxation of muscle tension (for which it is also of dubious efficacy). In their review of the literature in 1971, Greenblatt and Shader[6] found that in only 5 of 26 controlled double-blind studies was meprobamate clearly more effective than placebo, and in only one of ten controlled double-blind studies was it clearly more useful than a barbiturate. Given the equivocal efficacy and significant side effects of meprobamate, they concluded that its widespread use is irrational.

According to Goodman and Gilman[8] it is difficult to differentiate clinically between meprobamate and the barbiturates; only careful pharmacological analysis shows distinctions. Meprobamate is absorbed readily from the gastrointestinal tract; blood levels reach a peak within one or two hours and fall slowly over ten hours or more. The principal route of excretion is through the kidneys —90 percent emerges as an oxidized metabolite or a glucuronide. Like the barbiturates, mepro-

*David Jimerson, MD, Resident in Psychiatry.

bamate can induce the microsomal enzymes involved in drug metabolism.

The most common side effect of meprobamate is sedation; drowsiness is common at the typical dose of 400 mg four times a day. Psychological testing has shown some impairment of learning after an 800 mg dose and definite impairment of learning, motor coordination and reaction time after 1,600 mg. Hypersensitivity reactions occur in about 2 percent of patients, especially in persons with a history of dermatological or allergic problems, appearing most commonly as urticarial or intensely pruritic maculopapular and erythematous skin rashes. Other side effects include shaking chills and fever, nausea, vomiting, syncope and hypotension (particularly in elderly patients). Meprobamate is the only psychotropic agent other than the phenothiazines and tricyclic antidepressants known to produce significant incidence of hematological complications; these include thrombocytopenia, acute nonthrombocytopenic purpura, agranulocytosis (from which some fatalities have been reported), aplastic anemia and pancytopenia.

As to the risk of overdose, meprobamate is clearly less dangerous than the barbiturates, and just as clearly more dangerous than the benzodiazepine tranquilizers. In 1963, for example, psychotropic drugs were dispensed in approximately 46 million prescriptions; in that year there were 2,000 deaths from barbiturate overdoses and 79 from other psychotropic drug overdoses. The literature as of 1970 contained no cases of fatal poisoning by chlordiazepoxide, diazepam or oxazepam—but there had been 16 deaths from meprobamate in 720 reported cases of poisoning.[6]

In the first years after the clinical introduction of meprobamate there was considerable debate over the question of a physical withdrawal syndrome. A controlled double-blind study by Haizlip and Ewing[9] showed a withdrawal syndrome in 44 of 77 patients suddenly deprived of the drug after 3.2 or 6.4 grams every day for 40 days. Insomnia, vomiting, tremors, muscle twitches, anxiety, headache and ataxia developed in 30 of them. Three of them had from one to three convulsions within 36 to 48 hours. Psychotic behavior, at times resembling delirium tremens, developed in eight of the patients, but persisted no longer than three days despite lack of specific treatment. Other observers have rarely found a withdrawal syndrome in patients who received a median dose of 1.6 grams every day for an average of four months. Goodman and Gilman[8] recommend that meprobamate dosage not exceed 2.4 grams daily.

I agree with Dr. Braun that Mrs. Hull's seizure and subsequent confused behavior were related to withdrawal of the meprobamate. Because people addicted to hypnotic drugs typically give unreliable drug histories, the so-called pentobarbital intoxication test has become fairly common. In short, one observes the patient's tolerance to increasing doses of pentobarbital, estimates the 24-hour dose needed to maintain intoxication and then gradually withdraws the drug—at the rate of about 10 percent a day. There is cross-dependence among the various central nervous system depressant drugs, and pentobarbital—or more recently phenobarbital—is a commonly used withdrawal agent. The therapeutic blood level for meprobamate is 1 mg per 100 ml, and 6 to 10 mg per 100 ml is generally associated with coma. In Mrs. Hull's the blood level of 4.2 mg per 100 ml probably affected her driving and gives a clue to the severity of her addiction.

Dr. Gerner:* Some important points come up here. This lady apparently did have a severe depression, and I am thinking that she may have been misdiagnosed initially. Regardless of her case, however, I wonder if misdiagnosing and mistreating psychiatric disorders might not someday come into the same category as misdiagnosing and mistreating things like ulcers, appendicitis or brain tumors, and whether or not more consideration should be given to this by nonspecialists. Perhaps those patients whom practitioners treat chronically without finding the causes of their problems should be referred to a specialist. It seems to me that some drugs probably should not be allowed on the general market, or if they are they should be allowed to be prescribed only by certain physicians. For example, 5-fluorouracil is given only by specialists and only in certain situations. Yet other potentially dangerous drugs like glutethimide and meprobamate are dispensed almost indiscriminately. Only two drugs are really good for sleep, chloral hydrate and fluorazepam hydrochloride; the rest, although often prescribed for insomnia, destroy sleep insofar as we can measure. I wonder whether these potentially dangerous drugs (perhaps not chlordiazepoxide or diazepam because they are relatively safe) should be prescribed by doctors who are not specializing in the health of the mind and the emotions.

*Robert Gerner, MD, Resident in Psychiatry.

DR. MORRISON: One of the most common misdiagnoses is to mistake anxiety neurosis for depression or vice versa. Very often when patients have moderate depression we see only the anxiety and do not look underneath it for the depression. This woman is an excellent case in point. She apparently had some depressive symptoms for at least ten years, which became notably worse during the six months preceding this admission.

DR. HUEY:* *What about an involutional depression?*

DR. MORRISON: The phrase involutional melancholia pretty much went out with insulin coma treatment; many patients who have primary affective disorder show up for the first time during the involutional period with depression, but there is nothing particularly different about them with regard to family history, response to treatment, and so on.

DR. BRAUN: I do think that Mrs. Hull's tubal ligation represented a significant loss for her, and the family corroborates that her symptoms became noticeable about that time.

DR. NEMIROFF:† I would like to address Dr. Braun's question about where to go from here. I think it would be dangerous at this point to decide that this woman is over her problem, in view of her addiction and her apparently lifelong problem with dependency needs. She still needs support and someone to work with, yet she is becoming resistant to continuing therapy. I suggest confronting her gently with her dependency needs and the way she handles them to see if that would encourage her to continue follow-up psychotherapy and give you the opportunity to monitor her antidepressant medication for a while longer. I think it would be a mistake to cut off that medication prematurely.

DR. BRAUN: Yes, and I think that continuing the marital therapy is also of paramount importance. I have advised the Hulls to get that kind of help nearer home; they have too much of an excuse not to get it here because of the distance. Unfortunately, Mr. Hull is not amenable to further counseling.

DR. HUEY: *How do you think her coming to this grand rounds is going to affect your relationship with her in ongoing therapy?*

DR. BRAUN: We have been working with this for two months; it was not something that I sprang on her last week. She perceives it as something she wanted to do for me, much as she does things for other people.

DR. MORRISON: In retrospect, then, we have a patient who may have been treated more or less appropriately with minor tranquilizers, according to the original diagnosis, but the results in this case were disastrous. Her abuse of meprobamate along with her anxiety apparently masked an underlying affective disorder. Withdrawal of the medication led to a convulsion which may have in fact partially "treated" her affective disorder, leaving her in an almost hypomanic state. She was finally treated with antidepressant medication, and today she appears to be much better.

Usually in the neuroses or psychiatric illnesses like schizophrenia or personality disorder we do not expect to see dramatic personality changes, although there may be accentuation of previously existing traits. When confronted with a patient who exhibits sudden personality change as Mrs. Hull did, we need to look for a tumor or other organic causes, for affective disorder (in which the changes are easily recognized by the family and by the patient) and of course for the abuse of alcohol or some other substance.

This woman does present a problem in differential diagnosis. Does she have anxiety neurosis with a secondary depression, or does she have an illness more closely allied with the affective disorders, with episodic attacks of anxiety as part of that? We cannot be sure. Woodruff[3] noted that in patients in whom both conditions developed, there was essentially no difference in the phenomena of their illnesses. He did not feel that it was important to distinguish between patients with and patients without affective disorder. I think, however, that in determining treatment we have to look for the depression, and if we find it we have to treat it—as Dr. Braun has done.

*Leighton Huey, MD, Chief Resident in Psychiatry.

†Robert Nemiroff, MD, Assistant Clinical Professor of Psychiatry.

REFERENCES

1. Lader MH (Ed): Royal Medico-Psychological Assoc Studies in Anxiety. Ashford Kent, World Psychiat Assoc and Headley Bros Ltd, 1969
2. Wheeler EO, White PD, Reed ER, et al: Neurocirculatory asthenia, anxiety neurosis, effort syndrome, neurasthenia. JAMA 142:878-888, 1950
3. Woodruff RA Jr, Guze SB, Clayton PJ: Anxiety neurosis among psychiatric outpatients. Compr Psychiat 13:165-170, 1972
4. Winokur G, Holeman E: Chronic anxiety neurosis: Clinical and sexual aspects. Acta Psych Scand 39:384-412, 1963
5. Slater E, Cowie V: The Genetics of Mental Disorders. London, Oxford Univ Press, 1971
6. Greenblatt DJ, Shader RI: Meprobamate: A study of irrational drug use. Am J Psychiat 127:1297-1303, 1971
7. Weatherall M: Tranquilizers. Br Med J 1:1219-1224, 1962
8. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. New York, The Macmillan Co., 1970
9. Haizlip TM, Ewing JA: Meprobamate habituation. N Engl J Med 258:1181-1186, 1958

Refer to: Myasthenia gravis and the thymus gland—Medical Staff Conference, University of California, San Francisco. West J Med 123:123-127, Aug 1975

Medical Staff Conference

Myasthenia Gravis and the Thymus Gland

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SHOHET:* *Medical Grand Rounds this morning will be given by Dr. Robert Layzer, Associate Professor of Neurology. Dr. Layzer is in charge of both the Muscle Clinic and the Neurology Clinic, and he is going to talk about the role of the thymus gland in myasthenia gravis.*

DR. LAYZER:† Thank you. In order to illustrate the role of the thymus gland in myasthenia gravis, I would like to present the case of a patient whom we saw at this hospital. Mrs. Y is a 52-year-old woman who consulted me in September, 1972, because of difficulty swallowing, which had persisted for about two years. She also complained that her speech was nasal and hard to understand. There had been no ptosis or diplopia. A diagnosis of myasthenia gravis had been made, and the patient had been treated with anticholinesterase medicines. There was response to treatment at first, but as time went by it became increasingly difficult for the patient to maintain necessary nutrition. One month before admission to the hospital, while she was in Europe, the symptoms worsened and the patient began to lose weight. Returning home, she entered this hospital on September 25, 1972.

On examination the findings were restricted to the cranial nerves. There was mild weakness of the face and tongue. She was able to close her jaws strongly, but her voice was nasal, she was not able to swallow without choking and liquids sometimes came out of her nose. Adjustment of the dosage of anticholinesterase medicines did not help, and nasogastric tube feeding was required. Accordingly, about one month after admission, surgical removal of the thymus gland was carried out. The thymus gland had a normal gross appearance but contained an excessive amount of lymphocytic tissue in the form of germinal centers. After the operation there was improvement for a few days but then nasogastric feedings again were required. Prednisone was given in doses of 100 mg and 50 mg on alternate days. Within a few days the patient began to improve, and after two weeks there were almost no signs of myasthenia. She left the hospital and over the next year the dose of prednisone was gradually reduced. The

*Stephen B. Shohet, MD, Associate Professor of Medicine.
†Robert B. Layzer, MD, Associate Professor of Neurology.

myasthenic symptoms remained in abeyance, and the patient has been living an extremely active life without treatment for one year.

There are three major topics to be considered in a discussion of myasthenia gravis. One is the nature of the neurophysiological defect; for instance, whether the neuromuscular block is presynaptic or postsynaptic. We will not discuss that question this morning. The second topic, which will be the focus of my comments, is the pathogenesis of myasthenia, and particularly its relationship to an abnormality of the thymus gland; why removal of the thymus gland may be followed by improvement, and what is the role of disturbed immune mechanisms in myasthenia. The third topic, which I will touch on briefly, is the treatment of myasthenia gravis, a subject that relates closely to the problem of pathogenesis.

TABLE 1.—*Overall Results of Thymectomy in 267 Patients Without Thymoma Followed for Between 1 and 28 Years after Operation**

	Men		*Women*		*Total*	
Results	*Number*	*Per-cent*	*Number*	*Per-cent*	*Number*	*Per-cent*
Remission	15	30	77	36	92	35
Improvement	19	38	90	42	109	41
No change	6	12	13	6	19	7
Worse	2	4	3	1	5	2
Died	7	14	31	14	38	14
Lost to follow-up	1	2	2	1	4	1
Totals	50		217		267	

*Reproduced by permission from Perlo VP, et al.[1]

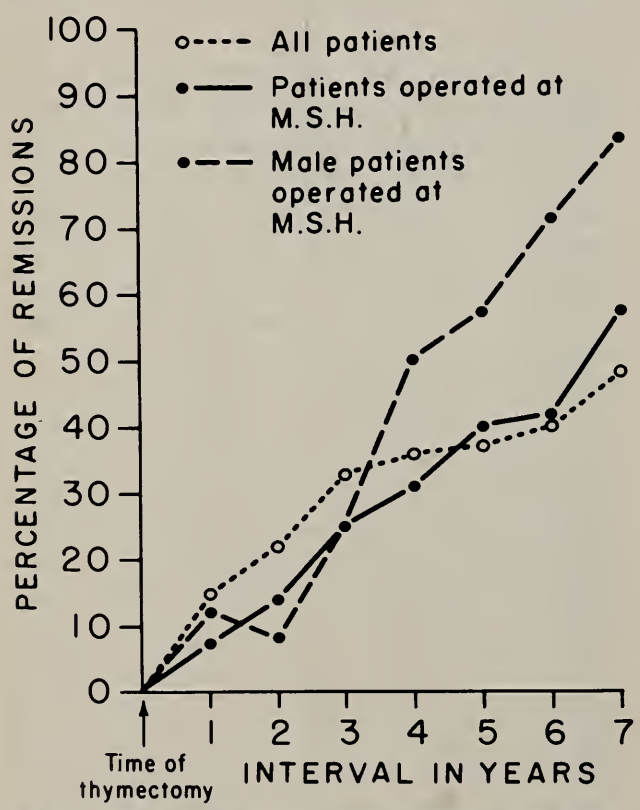


Chart 1.—Percentage of remissions in the first seven years after thymectomy. (Reproduced by permission from Papatestas AE, et al.[2])

The disease myasthenia gravis was given clinical definition in the 1870's and 1880's. Soon afterward, in 1910, Laquer and Weigert found a thymoma, a tumor of the thymus gland, in a postmortem examination of a patient with myasthenia. In 1911, Sauerbruch carried out a thymectomy for the treatment of thyrotoxicosis in a patient with myasthenia. Although the thyrotoxicosis did not improve, the myasthenic symptoms did. It was not until 1936, however, that Blalock revived interest in thymectomy in myasthenia gravis by removing a thymoma from a patient with myasthenia and noticing that the myasthenia improved. Blalock was encouraged to repeat the operation in other patients, and in 1944 he reported the results of 20 thymectomies in patients with myasthenia gravis. Most of the patients improved, and only two had tumors of the thymus gland. Since that time thymectomy has been done increasingly and with increasing confidence in patients with myasthenia gravis. In the past 20 years, thanks to improved methods of postoperative care, especially through the use of respiratory care units, thymectomy has become a relatively safe procedure.

Unfortunately, when we try to assess the results of thymectomy, we are hampered by the fact that no controlled study has ever been done and probably never will be done. Nevertheless, there is general agreement that patients treated by thymectomy fare better than untreated ones. Table 1 shows the combined results of thymectomy in 267 myasthenic patients without thymoma from the Massachusetts General Hospital and the Mt. Sinai Hospital of New York, who were followed for periods from 1 to 28 years.[1] Seventy-six percent of patients improved, with remission in nearly half of them. The death rate was 14 percent, mostly in the first four years and mostly in patients who had severe myasthenia initially. Some of the old generalizations about which patients were likely to benefit from thymectomy have not been sustained. Neither age, sex nor the duration of symptoms before surgical operation seem to affect the outcome. However, there are few statistics for patients over the age of 50, and operation is not usually recommended in patients over the age of 60 without a thymoma. The operative mortality

from thymectomy is close to zero in experienced centers.

Chart 1 shows a curious feature of the remissions that occur after thymectomy—the percentage of patients in remission increases for at least seven years after operation. (The data are from the Mt. Sinai Hospital.[2]) About 50 percent of survivors were in remission seven years after operation. The combined results from the Massachusetts General Hospital and Mt. Sinai Hospital show that remissions continue to occur even up to ten years after operation.[1] On the other hand, only 10 percent of patients go into remission in the first postoperative year.

In view of these results, it seems appropriate to do thymectomy in myasthenia whenever the disease is sufficiently disabling to warrant it. A patient should have more than purely ocular myasthenia, should not be older than about 60 years and should have good general health. It seems reasonable that surgical operation be done early because improvement may be delayed for many years.

The technique of thymectomy should be mentioned here. In some hospitals the sternum-splitting approach, which has been standard for many years, has been replaced by the less traumatic transcervical approach with results said to be just as good.[2] Nevertheless, in this hospital we still use the older method, feeling that it gives better visualization with less risk of leaving thymic tissue behind.

What is this mysterious benefit that takes seven years to reach a 50-percent remission rate and rarely produces remission in the first year? What is the role of the thymus in myasthenia? The answers are not yet available, but let us review some of the evidence at hand. First of all, thymoma is strongly linked to myasthenia. This tumor occurs in about 10 percent of all patients with myasthenia. Looking at it the other way around, 30 percent of patients with thymoma have myasthenia gravis, although this figure is a little weighted because patients with myasthenia are carefully scrutinized for the presence of thymoma. Table 2 lists some other diseases associated with thymoma. Some of these diseases also occur in association with each other, and each of them has appeared at one time or another in association with both myasthenia and thymoma, except for Cushing's syndrome. But myasthenia is rarely linked with these other diseases, and the lymphoepithelial type of tumor found in myasthenia is not the type usually associated with other diseases.

TABLE 2.—*Disorders Sometimes Associated with Thymoma*

Myasthenia Gravis
Aregenerative Anemia (Leukopenia, Thrombocytopenia)
Hypogammaglobulinemia
Cushing's Syndrome
Pemphigus
Autoimmune Hemolytic Anemia
Lupus Erythematosus and Other Connective Tissue Diseases
Polymyositis, Myocarditis
Chronic Mucocutaneous Candidiasis

In patients with myasthenia in whom there is not a tumor, the thymus often shows abnormal proliferation of the lymphoid elements with formation of germinal centers in the thymic medulla, a change which has been termed thymic hyperplasia.[3] Germinal centers have been said not to occur in normal thymic tissue, but in an autopsy study of patients who died in accidents, 70 percent of thymuses showed at least one germinal center.[4] However, germinal centers are more numerous in the thymic medulla in persons with myasthenia than in normal persons; they have also been found in lupus erythematosus and in other connective tissue diseases.[5] In elderly patients with myasthenia the thymus gland often does not contain any recognizable thymic tissue.[6]

Thus, myasthenia is strongly linked with frank pathology of the thymus gland. Why, then, does it take so long before a patient benefits from thymectomy? Why is removal of a neoplastic thymus gland less often followed by improvement than removal of a nontumorous gland? Why does myasthenia sometimes appear for the first time *after* a tumor of the thymus gland has been removed, even a year or two later?[7] These questions still have not been answered satisfactorily. Several hypotheses have been put forward to account for the role of the thymus in myasthenia, and we can examine these in turn.

An early idea was that the thymus secreted a substance that caused myasthenia. Support for this idea came from the clinical observation that 10 to 30 percent of the babies born to mothers with myasthenia suffer from neonatal myasthenia for a few weeks after birth. This neonatal myasthenia is always transient. It is difficult to escape the conclusion that some circulating maternal substance crosses the placenta to cause myasthenia in the baby, but the substance, if it exists, has proved to be very elusive.

During the 1940's, Andrew Wilson in England obtained, from both human and whale thymus glands, small amounts of a substance that produced neuromuscular block, but this research came to nothing (although a similar achievement, as we will see, was recently reported by Goldstein). In 1960, Simpson in Scotland announced the novel hypothesis that myasthenia is an autoimmune disease.[8] Simpson pointed out an association between myasthenia and other diseases suspected to have an autoimmune pathogenesis, such as rheumatoid arthritis and pernicious anemia. (Rowland and his colleagues, on the other hand, found that myasthenia is rarely associated with other diseases except for the well-known association with thyrotoxicosis.[9]) Simpson suggested that myasthenia might be caused by circulating antibodies against the acetylcholine receptor in the motor end plate. Curiously enough, just at that time Nastuk at Columbia University, with a medical student named Arthur Strauss, was looking for a neuromuscular blocking substance in myasthenic serum. They discovered that some myasthenic sera had a cytopathic effect on their muscle preparations. Nastuk and Strauss subsequently identified the cytopathic serum factor as an antibody.[10] With the fluorescent antibody technique, these antibodies react with the cross striations of skeletal muscle; by electron microscopy it appears that the antibodies react with sarcoplasmic reticulum at the I bands. This kind of antibody is present in the serum of 30 percent of patients with myasthenia who do not have a thymoma, but is found in the serum of almost all patients with myasthenia who do have a thymoma. It is also present in a quarter of patients with thymoma who do not have myasthenia.[11] The reason that muscle antibodies occur in patients with thymoma was suggested by the discovery that these antibodies also react with certain cells in the thymus called myoid cells.[12] As their name suggests, these muscle-like cells have cross striations, contain myofibrils and are, in effect, little muscle cells.

Here then is another important link between myasthenia and the thymus—antibodies that cross-react with muscle and thymus. Unfortunately, the antibodies do not seem to be the right kind to cause myasthenia. In the first place, they do not seem to be the factor that crosses the placenta to cause neonatal myasthenia, for they may be absent from the serum of the mothers who have babies with neonatal myasthenia, and may be present in mothers who give birth to unaffected babies.[13] Second, the antibodies do not react with the end plate region of muscle, the site of altered function in myasthenia. Attempts to detect antibody bound to the neuromuscular junction in myasthenia have also been unsuccessful.[14]

In the laboratory, however, an interesting experimental model of myasthenia was recently produced by immunizing rabbits with purified acetylcholine receptor prepared from the electric organ of Electrophorus electricus. In the rabbits, antibodies against the acetylcholine receptor were produced, and these antibodies blocked the rabbits' own receptors, causing severe weakness that could be reversed by administration of anticholinesterase drugs.[15] In these elegant experiments, the antibody can be likened to pharmacological agents like curare or bungarotoxin, which also react specifically with the acetylcholine receptor and produce weakness. Several laboratories are now searching for similar antibodies in serum from patients with myasthenia.[16]

As knowledge of immune mechanisms increased, another autoimmune theory of myasthenia became current. It was proposed that myasthenia is a disease of cellular immunity, and that a clone of immune lymphocytes somehow produces the neuromuscular block. This mechanism could explain why the effect of thymectomy may be delayed for so long, since lymphocytes which are capable of causing disease may remain in circulation after thymectomy. The role of the thymus in initiating or perpetuating the disease might then be correlated with the known function of the thymus in regulating the immune function of lymphocytes. There is little direct evidence for this theory, but support recently has been provided by two reports describing the effects of prolonged thoracic duct lymph drainage in five patients with myasthenia.[17,18] All five patients improved, some of them strikingly, and weakness returned a few days after the procedure was stopped. The pathogenetic role of lymphocytes in myasthenia needs to be better defined.

Finally, I would like to describe the Goldstein hypothesis.[19] Gideon Goldstein suggested that the pathology of the thymus gland in myasthenia resembled that of autoimmune thyroiditis (Hashimoto's disease). He called this process autoimmune thymitis, and he suggested that the damaged thymus gland leaked a protein substance (not an antibody) into the blood and that this substance was capable of causing neuromuscular block. To support this theory, he produced an experimental

model by immunizing animals with thymus gland and testing neuromuscular transmission by repetive nerve stimulation. He reported that immunized animals showed an abnormal decline in the amplitude of evoked muscle action potentials although the animals did not become weak. Several other investigators have been unable to reproduce these results, and Goldstein's theory has therefore not met with wide acceptance. Recently Goldstein isolated from the thymus tissue two polypeptides (which he named thymin I and II) said to have neuromuscular blocking properties. When these peptides were assayed for their ability to produce neuromuscular blockade, it appeared that 4 μg of thymin reduced the evoked muscle action potential to about 85 percent of the initial value, but larger amounts of thymin caused no further decline in response.[20] This dose response curve is difficult to interpret and casts doubt on the relevance of thymin to the pathogenesis of myasthenia although the peptides appear to have some influence on immune mechanisms.

Despite tantalizing hints, therefore, we do not really understand the role of the thymus in myasthenia or why some patients take so long to benefit from thymectomy. In seriously ill patients who have not responded to thymectomy, we are left with one other form of treatment, the one that was used in Mrs. Y's case, glucocorticosteroid therapy. High doses of corticosteroid medication produce excellent remission of weakness in nearly all cases, and usually the dose can be reduced in time to a tolerable maintenance level. If possible, it is best to carry out thymectomy before using steroids in order to improve the likelihood of achieving permanent remission. Of course, steroid therapy is a two-edged sword and should only be given to patients whose myasthenia is sufficiently disabling or life-threatening to warrant the risks of such treatment.

REFERENCES

1. Perlo V, Arnason B, Poskanzer D, et al: The role of thymectomy in the treatment of myasthenia gravis. Ann NY Acad Sci 183:308-315, Sep 15, 1971

2. Papatestas AE, Alpert LI, Osserman KE, et al: Studies in myasthenia gravis: Effects of thymectomy—Results on 185 patients with nonthymomatous and thymomatous myasthenia gravis, 1941-1969. Am J Med 50:465-474, Apr 1971

3. Castleman B: The pathology of the thymus gland in myasthenia gravis. Ann NY Acad Sci 135:496-505, Jan 26, 1966

4. Middleton G: The incidence of follicular structures in the human thymus at autopsy. Aust J Exp Biol Med Sci 45:189-199, Apr 1967

5. Mackay IR, DeGail P: Thymic "germinal centres" and plasma cells in systemic lupus erythematosus. Lancet 2:667, Sep 28, 1963

6. Perlo VP, Arnason B, Castleman B: The thymus gland in elderly patients with myasthenia gravis. Neurology 25:294-295, Mar 1975

7. Kimura J, Van Allen MW: Post-thymomectomy myasthenia gravis. Report of a case of ocular myasthenia gravis after total removal of a thymoma and review of literature. Neurology (Minneap) 17:413-420, Apr 1967

8. Simpson JA: Myasthenia gravis: A new hypothesis. Scot Med J 5:419-436, Oct 1960

9. Wolf SM, Rowland LP, Schotland DL, et al: Myasthenia as an autoimmune disease: clinical aspects. Ann NY Acad Sci 135: 517-535, Jan 26, 1966

10. Strauss AJL, Seegal BC, Hsu KC, et al: Immunofluorescence demonstration of a muscle binding, complement-fixing serum globulin fraction in myasthenia gravis. Proc Soc Exp Biol Med 105:184-191, Sep 1960

11. Strauss AJL, Smith CW, Cage GW, et al: Further studies on the specificity of presumed immune association of myasthenia gravis and consideration of possible pathogenic implications. Ann NY Acad Sci 135:557-579, Jan 26, 1966

12. Van der Geld HWR, Strauss AJL: Myasthenia gravis: immunological relationship between striated muscle and thymus. Lancet 1:57-60, Jan 8, 1966

13. Oosterhuis HJGH, Feltkamp TEW, Van der Geld HRW: Muscle antibodies in myasthenic mothers and their babies. Lancet 2:1226-1227, Dec 3, 1966

14. McFarlin DE, Engel WK, Strauss AJ: Does myasthenic serum bind to the neuromuscular junction? Ann NY Acad Sci 135:656-663, Jan 26, 1966

15. Patrick J, Lindstrom J: Autoimmune response to acetylcholine receptor. Science 180:871-872, May 25, 1973

16. Almon RR, Andrew CG, Appel SH: Serum globulin in myasthenia gravis: inhibition of α-bungarotoxin binding to acetylcholine receptors. Science 186:55-57, Oct 1974

17. Bergström K, Franksson G, Matell G, et al: The effect of thoracic duct lymph drainage in myasthenia gravis. Europ Neurol 9:157-167, Mar 1973

18. Tindall SC, Peters BH, Caverley JR, et al: Thoracic duct lymphocyte depletion in myasthenia gravis. Arch Neurol 29:202-203, Sep 1973

19. Goldstein G: Myasthenia gravis and the thymus. Annu Rev Med 22:119-124, 1971

20. Goldstein G: Isolation of bovine thymus: A polypeptide hormone of the thymus. Nature 247:11-14, Jan 1974

Important Advances in Clinical Medicine

Epitomes of Progress—Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Telephonic Transmission of Electroencephalograms

THE TRANSMISSION of bioelectrical signals by telephone and radio is an established fact. Transmission of electrocardiograms by many hospitals around the United States and their computer interpretation is a daily telephonic activity. Low, Bennett, Schear and others have established the reliability of telephonic electroencephalogram (EEG) transmission. Considerable controversy among EEG experts has developed over the quality of such transmitted EEG tracings.

To understand this concern one must understand the procedure. Essentially, at the sending station (usually a small hospital), a hospital employee pastes 21 EEG plate electrodes on the surface of a patient's scalp and plugs these into a jack box transmitter which uses the EEG activity to modulate a kilo Herz signal. By telephone wire the signal is received at the receiving station, demodulated and played out on a standard EEG machine. The receiving station technician may interrupt the transmission at any time to ask the sending station technician to make any necessary corrections to produce a satisfactory record.

An axiom in electroencephalography is that the quality of an electroencephalographic interpretation is directly related to the quality of the EEG record produced by the EEG technologist. The technologist is the key to good electroencephalography.

Note that when the sending person is a multidisciplinary technician and transmits only two or three records a week, he or she may not become competent in attaching EEG electrodes properly and at the proper scalp locations. In one widely used system there is no comparative record recorded at the sending site; the sending technician never sees the record he is transmitting. The salient doubt raised by many, but not all, electroencephalographers is whether or not such a person is capable and competent to transmit electroencephalographic signals. If the transmitting technician is trained in electroencephalography and understands the basic fundamentals of elec-

troencephalographic quality and if a comparative EEG recording is made at the sending site simultaneously with the transmitted tracing, then there is no technical argument about telephonic EEG transmission.

In essence, then, there are two issues. (1) Can an untrained (or three-day trained) technician transmit adequate EEG signals? (2) Is it necessary to have a recording made at the sending hospital?

At this time there is no consensus on these points by the American Electroencephalography Society, the American Medical Electroencephalography Society or the Western Electroencephalography Society. Experienced electroencephalographers are divided in their opinions regarding the reliability of records transmitted by untrained technicians. In the United States there is a pronounced variability in the quality and reliability of portable electroencephalographic records. There is also an equally wide range in the interpretability of telephonic transmitted electroencephalographic tracings. Both systems can produce records equal to those from permanent EEG facilities—if the procedures are done properly.

In summary, though still somewhat controversial, telephonic EEG transmission as a method to extend EEG availability is being widely used and is a permanent addition to EEG technology.

J. M. MOSIER, MD

REFERENCES

Schear HE, Rowe WJ, Pori J: Telephonic transmission of electroencephalograms. Clin Electroencephalography 5:24-30, Jan 1974

Bennett D, Gardner R: Current status of EEG telephone telemetry. Clin Electroencephalography 5:8-23, Jan 1974

Low M: Conference on Telephonic EEG. Presented to the American Electroencephalography Society, Seattle, Aug 1974

The Dizzy Patient

ALTHOUGH THE SYMPTOM of dizziness continues to plague the physician because of its multiple causes, the presence of true vertigo will at least suggest an investigation of inner ear pathology or the vestibular central nervous system connections. In the evaluation of vertiginous patients, several new concepts have arisen within the last few years which deserve attention by all physicians:

1. The concept of "cervical vertigo" whereby neck lesions give rise to stimulation of the upper cervical nerve roots is a common entity. Symptoms of dizziness on movement of the head in all positions regardless of the body position is a clue and even tinnitus or slight muffling of hearing may be present, possibly from spasm of the middle ear muscles. Results of caloric tests are usually normal, and controversy exits as to whether mild eye movement abnormalities can be recorded by electronystagmography (ENG). Treatment with muscle relaxants, physical therapy or other measures aimed at correcting the local pathology will usually be successful while inner ear depressant drugs are rarely of benefit.

2. It is clear that previous syphilis can give rise to delayed inner ear pathology simulating Meniere's syndrome, usually bilaterally. This explosive and fluctuating combination of tinnitus, ear pressure and progressive hearing loss may progress to total destruction of the inner ears but there is evidence that corticosteroids may arrest the situation, this being one of the few causes of nerve deafness that is probably responsive to cortisone.

3. There is a phenomenon of a fistula or leak between the middle ear and inner ear that is often amenable to surgical intervention. Spontaneous fistulas may occur after sudden straining or coughing or descent in an aircraft if the patient has a cold. Symptoms usually include decreased hearing but in many patients there are fluctuating Meniere's-like symptoms and a careful history of a pressure-related event or injury occurring before the symptoms appear may lead to successful treatment through ear exploration.

4. Careful selection of patients for translabyrinthine labyrinthectomy has improved the results of surgical intervention in vertiginous states since simple oval window labyrinthectomy of the ear may lead to residual tissue that gives rise to persistent vertigo in 10 percent of cases. Selective vestibular nerve section is still worthwhile in some patients with refractory vestibular problems after vestibular neuronitis, head injury or even in severe postural vertigo. Selective sectioning of a small branch of the vestibular nerve to the posterior canal has been reported to relieve the annoying symptom of recurrent postural vertigo when the head is turned down and to the diseased side (Gacek).

5. Another new concept is the involvement of the inner ear by otosclerosis, rather than as a process that just fixes the stapes to the oval window to cause hearing loss. In such patients there may be a sensorineural hearing loss and intermittent vertigo. Diagnosis may be suggested by findings on detailed laminograms of the temporal

bones and is important since the process may be arrested by treatment with sodium fluoride in high doses.

Treatment of mild fluctuating vertigo with regular administration of meclizine has seemed more effective in this writer's experience than only using the drug intermittently when symptoms escalate. For the treatment of acute vertigo with severe vomiting, the drug droperidol (Inapsine®), used often after surgical operation, is a very powerful and effective vestibular suppressant. Also, McCabe has found that intravenous administration of diazepam (Valium®) is extremely effective for acute vertiginous crises.

JAMES R. NELSON, MD

REFERENCES

Biemond A, DeJong JMBV: On cervical nystagmus and related disorders. Brain 29:437-458, 1969

Patterson ME: Congenital leutic hearing impairment. Arch Otolaryngol 87:378-382, Apr 1968

Healy GB, Strong MS, Sampogna D: Ataxia, vertigo and hearing loss—A result of rupture of inner ear window. Arch Otolaryngol 100:130-135, Aug 1974

Isaacs' Syndrome

THE CLINICAL FEATURES of this rare syndrome include chronic, painful muscle stiffness, fasciculations and myokymia, often with associated muscle atrophy, weakness, excessive perspiration and increased basal metabolic rate. Age of onset ranges from the newborn period to the sixth decade, with the peak incidence in the second and third decades. Symptoms tend to be static or slowly progressive. Findings on an electromyogram show continual motor unit potentials in the involved muscles despite a voluntary effort to relax.

Isaacs and several subsequent investigators showed that muscle stiffness and electromyographic activity continued after spinal anesthesia or peripheral nerve block but were abolished by curare. This has been interpreted to indicate that the muscle symptoms are due to abnormal discharges at the termination of the nerves. Abnormal findings on nerve conduction studies, neuropathic changes noted in sural nerve and results of muscle biopsy studies more recently have been reported as further evidence suggesting an underlying peripheral nerve disorder.

Isaacs found that dipenylhydantoin (Dilantin®) ameliorated most of the symptoms. In some cases, refractory to diphenylhydantoin, patients have responded well to carbamazepine (Tegretol®). The experimentally shown capability of diphenylhydantoin to stabilize motor nerve terminals and muscle membranes may explain the therapeutic effectiveness of this drug.

J. CARROLL RAMSEYER, MD

REFERENCES

Isaacs H: Continuous muscle fiber activity in an Indian male with additional evidence of terminal motor fiber activity. J Neurol Neurosurg Psychiatry 24:126-131, Apr 1967

Wallis EW, Poznak AV, Plum F: Generalized muscle stiffness, fasciculations, and myokymia of peripheral nerve origin. Arch Neurol 22:430-439, May 1970

Welch LK, Appenzeller O, Bicknell JM: Peripheral neuropathy with myokymia, sustained muscular contraction, and continuous motor unit activity. Neurology 22:161-169, Feb 1972

Su PC, Feldman DS: Motor nerve terminal and muscle membrane stabilization by diphenylhydantoin administration. Arch Neurol 28:376-379, Jun 1973

Steroid Therapy of Myasthenia Gravis

CORTICOSTEROIDS have been used in the treatment of myasthenia gravis since the late 1940's. Most studies have concluded that steroid therapy led either to short-term benefit or, more commonly, to exacerbation of symptoms. Early observations were based on the administration of high doses given for brief periods. Recently the long-term use of appropriate doses of adrenocorticotropic hormone (ACTH) and adrenocorticosteroids has been found to be effective in suppressing the symptoms of the disease.

When large doses of steroids (100 mg) are given alone on alternate days, symptoms frequently exacerbate and patients become extremely weak—frequently requiring admission to hospital and occasionally tracheostomy for respiratory support. Worsening of symptoms can be either lessened or avoided altogether when prednisone is administered in 25 mg doses on alternate days while the patient is maintained on an effective dose of anticholinesterase medication. Subsequently, the dose of prednisone may be gradually increased while anticholinesterase medication is decreased until maximum symptomatic benefit is achieved. In some patients it may not be possible to reduce anticholinesterase medication significantly. The alternate day steroid treatment reduces the occurrence of untoward endocrinological side effects. Once the symptoms of myasthenia gravis have remitted, it may be possible to reduce and eventually stop anticholinesterase medication while maintaining the patient on smaller doses of

steroids. To date it has not been possible to determine the overall period of time necessary for patients to remain on steroid maintenance doses. As yet the effect of steroids on the disease process remains unknown.

Because of the potentially dangerous side effects resulting from long-term high doses of corticosteroids, this mode of therapy should be used only when the classical treatment with anticholinesterase agents or thymectomy or both have failed to control the symptoms of the disease.

N. VIJAYAN, MD
P. M. DREYFUS, MD

REFERENCES

Warmolts JR, Engel WK: Benefit from alternate day prednisone in myasthenia gravis. N Engl J Med 286:17-20, Jan 1972

Seybold ME, Drachman DB: Gradually increasing doses of prednisone in myasthenia gravis reducing the hazards of treatment. N Engl J Med 290:81-84, Jan 1974

Dantrolene Sodium (Dantrium®-Eaton) for Relief of Spasticity

WITHIN THE last three years, extensive evaluation of dantrolene sodium (Dantrium®), a unique chemical agent for relief of severe spasticity, has been done. This medication appears to act directly on the contractile mechanism of skeletal muscle rather than as a central suppressant of spinal cord or higher brain stem reflexes concerned with the spastic state. It is believed that the drug interferes with the release of calcium from the sarcoplasm and thus interferes in the excitation-contraction sequence of muscle. Results of experimental studies have shown diminution of the Achilles reflex and resting tone; while in some reports, volutional contraction of the muscle as measured by transducers or as monitored by electromyography was little affected. The drug offers the potential of decreasing spasms in patients with cerebral palsy, spinal injuries or multiple sclerosis. Findings of recent clinical studies indicate an approximate 50 percent improvement in most patient groups, although with considerable variability from one report to the next.

Side effects include pronounced diarrhea, occasional vertigo and rare hepatic dysfunction. General malaise, light-headedness and some confusion also may occur. Many patients have as a side effect such increased weakness that use of the drug must be discontinued. The drug's effect usually is short-lived and the dose must be increased gradually from 25 mg twice a day to as much as 100 mg four times a day. The drug apparently is not effective for painful muscular contraction in various rheumatic states.

It appears that the dantrolene sodium may be worth trying in patients whose progress in recovery from illnesses with spasticity has not been complete, but at the risk of inducing some simultaneous decrease in motor strength. Landau has recently attacked the theoretical concepts in the use of such agents since he believes that suppression of motor unit activity in symptomatic hyperactive reflexes usually would have to interfere with purposeful movement as well. He points out that previous trials of curare for the relief of reflex spasm are effective but exaggerate weakness.

Despite the theoretical controversies about the new drug, it deserves further study. The dose must be carefully determined for each patient and further data concerning long-term toxicity are needed before its proper place in the armamentarium of relaxant drugs is assigned.

JAMES R. NELSON, MD

REFERENCES

Chyatte SB, Basmajian L: Dantrolene sodium's long-term effects and severe spasticity. Arch Phys Med Rehabil 54:311-315, Jul 1973

Chyatte SB: Dantrolene sodium and athetoid cerebral palsy. Arch Phys Med Rehabil 54:365-368, Aug 1973

Brain-stem Audiometry

IT IS NOW possible to record in humans the electrical activity generated along the auditory pathway in its course from the cochlea to the cortex using surface electrodes (Jewett). The principle employed is that of "far-field" recording and entails using a small computer to average the potentials generated—at a distance out of the background electrical noise. Approximately 1,000 to 2,000 click trials presented at 10 per second are necessary to resolve the brain-stem components.

With this technique, it is possible to define a series of seven deflections in the first ten milliseconds following click signals. Their amplitudes are in the nanovolt range. Both the latency and amplitude of the components vary in an orderly manner with signal intensity and can be detected to click signals close to threshold intensity. The generators of these potentials have been shown by experiments in animals (Jewett) and in humans (Starr and Achor) to originate in particular areas of the auditory pathway. For instance, Wave I,

which occurs at the shortest latency (1.5 milliseconds), appears to be generated by VIII nerve activity. Whereas, Wave V which appears at latency of about 5.5 milliseconds, appears to be generated in the region of the inferior colliculus. Factors of attention, arousal or expectation do not affect the amplitude or latencies of the response (Picton).

The ability to record the activity of the auditory pathway from a surface electrode in human subjects affords the physician a new tool for evaluating (1) the presence or absence of hearing by objective means, (2) some idea as to the extent of hearing impairment by changes in latency or amplitude of the responses and (3) a measure of the functioning of the central auditory pathway in various neurological diseases.

ARNOLD STARR, MD

REFERENCES

Jewett DL: Volume conducted potentials in response to auditory stimuli as detected by averaging in the cat. Electroencephalogr Clin Neurophysiol 28:609-618, Jun 1970

Picton TW, Hillyard S: Human auditory evoked potentials—II. Effects of attention. Electroencephalogr Clin Neurophysiol 36: 191-200, Feb 1974

Starr A, Achor LJ: Auditory brainstem responses in neurological disease. Arch Neurol, (In Press)

Diet in Multiple Sclerosis

CONSIDERATION OF nutritional factors has always been prominent in the search for the cause and proper treatment of multiple sclerosis (MS). Deficiencies of vitamins and minerals, food allergies and fat intake have been suggested as possible etiologic factors but have never been confirmed as significant. Treatment with vitamin B-12 (and with niacin), as with numerous drugs, was initially thought promising but has faded from use (popularity). Swank's success with a low fat diet has been neither confirmed nor contradicted. Similar but less physiological dietary regimes, based only on anecdotal reports, have recently been popularized in the lay press. The unpalatable nature of these diets makes it unlikely that many patients will stay on them long enough to build up a pool of scientifically significant statistics.

Findings from epidemiological studies related to nutrition have shown significant correlation only with total fat intake and with the percent of calories of animal origin. These are in accord with the geographic findings of high risk areas in countries where the use of dairy products (animal fats) is high.

At present it does not seem that nutritional factors play an important part in either the cause or the treatment of MS, although one double-blind study suggested that a supplement of linoleate (sunflower seed oil was the source) decreased the severity, duration and perhaps the frequency of exacerbations. Even though it is not certain that a high fat diet may have an unfavorable effect on MS, it still seems reasonable to advise MS patients to eat a low fat diet, and to avoid dietary extremes and indiscretions.

GUY M. HUNT, MD

REFERENCES

Schumacher GA: The demyelinating diseases, chap 25, *In* Baker AB, Baker LH (Eds): Clinical Neurology, Revised Ed. Hagerstown, MD, Harper and Row, 1974, pp 6-46

Alter M, Yamour M: Multiple sclerosis prevalence and nutritional factors. Am Trans Am Neurol Assn 98:253-254, 1973

Rose AS: Multiple sclerosis, a clinical and theoretical review. J Neurosurg 41:279-284, Sep 1974

Millar JHD, Zilkha KJ, Langman MJS, et al: Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. Br Med J 1:765-768, Mar 31, 1973

Guanidine Hydrochloride Therapy in Neuromuscular Disorders

GUANIDINE HYDROCHLORIDE facilitates acetylcholine release at the neuromuscular junction. The drug was first used in treating patients with myasthenia gravis in the late 1930's but was found to be ineffective. In some patients treated, weakness increased. However, in most patients with the myasthenic syndrome (Eaton-Lambert), guanidine decreases weakness and repairs the electrophysiologically demonstrable defect of neuromuscular transmission. The drug also has proven beneficial in some patients with botulinum intoxication. Evidence is far from convincing that guanidine significantly alleviates symptoms in patients with amyotrophic lateral sclerosis even temporarily, and the natural course of the disease is not altered by this therapy.

Adverse reactions to guanidine hydrochloride are common and may be serious. Side effects range from paresthesias, tremors, ataxia, nystagmus, slurred speech, vertigo, increased weakness, increased emotionality, anorexia, nausea, diarrhea, various skin eruptions, anemia, leukopenia, thrombocytopenia or aplastic anemia. Monthly blood counts on patients treated with guanidine appear to be sufficiently sensitive to detect the slowly developing bone marrow depression.

Guanidine hydrochloride is not listed in the Physician's Drug Reference and The American Hospital Formulary Service. The drug is supplied as a 125 mg tablet only and the dosage must be carefully tailored to individual patients.

In summary, guanidine hydrochloride is clearly indicated in the treatment of patients with the myasthenic syndrome and probably has some usefulness in botulinum intoxication, but it is ineffective in amyotrophic lateral sclerosis. Monthly blood counts on patients treated with this drug are mandatory. The high incidence of potentially serious adverse reactions and the as yet unproven value in the treatment of other neurologic disorders strongly mediate against indiscriminate use of guanidine in other conditions except the two listed above.

W. C. WIEDERHOLT, MD

REFERENCES

Otsuka M, Endo M: The effect of guanidine on neuromuscular transmission. J Pharmacol Exper Ther 128:273-282, 1960

Elmqvist D, Lambert EH: Detailed analysis of neuromuscular function in a patient with the myasthenic syndrome sometimes associated with bronchogenic carcinoma. Mayo Clin Proc 43: 689-713, Oct 1968

Cherington M, Ryan DW: Botulism and guanidine. N Engl J Med 278:931-933, Apr 1968

Norris FH Jr, Calanchini PR, Fallat RJ, et al: The administration of guanidine in amyotrophic lateral sclerosis. Neurology (Minneap) 24:721-728, Aug 1974

Current Therapy of Parkinson's Disease

SINCE COTZIAS reported the dramatic therapeutic effectiveness of levodopa in 1969, this drug has rapidly and rightfully become the cornerstone of treatment of Parkinson's disease. However, long term follow-up of patients treated with levodopa shows that this form of therapy is far from ideal.

In most patients, maximal reduction of disability is shown during the first year of treatment, with gradual progression of symptoms over the next four years so that many patients are as disabled after five years of levodopa therapy as they were initially. On the other hand it seems clear that chronic levodopa therapy does reduce mortality and severe disability in Parkinson's disease. It should also be recognized that most of these patients are elderly and it is often difficult, in long-term observation, to accurately distinguish symptoms due to aging from symptoms due to progression of Parkinson's disease.

Patients on long-term levodopa often require adjustment of dosage as a function of therapeutic response and the nature and severity of side effects. In a large number of patients, the amount of levodopa which can be tolerated is limited by a unique choreathetosis, which is usually clearly dose-related. Nausea, often dose-related also, is the most common side effect and, if persistent, may prevent maximal levodopa benefit. If the peripheral decarboxylation of levodopa is prevented by a dopa decarboxylase inhibitor (which does not pass the blood-brain barrier), only about 20 percent of the usual amount of levodopa is required to produce a therapeutic effect. A fixed combination tablet containing 10 mg of such an inhibitor, carbidopa, and 100 mg of levodopa is associated with much less nausea but no less choreathetosis than levodopa alone. This drug combination is scheduled to be marketed soon under the trade name Sinemet®. After two or three years of levodopa therapy some patients develop rapid hour-to-hour fluctuation in motor performance, the "on-off" effect. Cotzias and his colleagues have recently reported that a regimen consisting of a low protein diet (0.5 gram per kg of body weight per day), levodopa and a peripheral dopa decarboxylase inhibitor will reduce the severity of this troublesome symptom.

The incidence of progressive dementia is roughly 30 percent to 40 percent in patients on long-term levodopa therapy. Such dementia is not considered related to the levodopa but seems rather a common feature of Parkinson's disease which was previously not adequately appreciated.

Many patients benefit from administration of older anticholinergic drugs such as trihexyphenidyl (Artane®) and benztropine (Cogentin®) in addition to levodopa. Amantidine hydrochloride (Symmetrel®) is another effective drug, sometimes given alone or with an anticholinergic drug, but usually as an adjunct to levodopa. In occasional, carefully selected patients who are severely disabled by tremor and rigidity in spite of drug therapy, unilateral stereotaxic thalamotomy may still be considered.

J. CARROLL RAMSEYER, MD

REFERENCES

Markham CH, Treciokas LJ, Diamond SG: Parkinson's disease and levodopa—A five year follow-up and review (Medical Progress). West J Med 121:188-206, Sep 1974

Sweet RD, McDowell FH: Plasma dopa concentrations and the "on-off" effect after chronic treatment of Parkinson's disease. Neurol 24:953-956, Oct 1974

Markham CH, Diamond SG, Treciokas LJ: Carbidopa in Parkinson disease and in nausea and vomiting of levodopa. Arch Neurol 31:128-133, Aug 1974

Mena I, Cotzias GC: Protein intake and treatment of Parkinson's disease with levodopa. N Engl J Med 292:181-184, Jan 1975

ADVISORY PANEL TO THE SECTION ON NEUROLOGY

EDWARD H. DAVIS, MD, *Chairman, Beverly Hills*

JAMES R. NELSON, MD
CMA Section on Neurology
Chairman
La Jolla

PIERRE DREYFUS, MD
CMA Section on Neurology
Secretary
University of California, Davis

HOWARD SIEDLER, MD
CMA Section on Neurology
Assistant Secretary
Kentfield

ROBERT I. PODOSIN, MD
CMA Scientific Board
Los Angeles

J. CARROLL RAMSEYER, MD
Los Angeles

GUY M. HUNT, MD
Loma Linda University

DAVID PRINCE, MD
Stanford University

ARNOLD STARR, MD
University of California, Irvine
California College of Medicine

RICHARD D. WALTER, MD
University of California, Los Angeles

WIGBERT WIEDERHOLT, MD
University of California, San Diego

BRUCE BERG, MD
University of California, San Francisco

J. P. VAN DER MEULEN, MD
University of Southern California

BYRON C. PEVEHOUSE, MD
San Francisco

DAVID JOHNSON, MD
Orange

STANLEY VAN DEN NOORT, MD
University of California, Irvine

MAIRE MCAULIFFE, MD
San Francisco

MICHAEL OLDSTONE, MD
La Jolla

JACK M. MOSIER, MD
Long Beach

EDITORIALS

Combination Antimicrobial Therapy

In the third annual Henry Brainerd Memorial Lecture, published in this issue of the Journal, Jawetz reviews the pros and cons of combination antimicrobial therapy and attempts to assess the role of this modality in the treatment of infection.

All would agree that using more than one drug where one would suffice is wasteful, expensive and potentially hazardous. The dangers are that in patients receiving more than one drug, superinfections are more likely to develop and there is greater risk of toxic or allergic side effects. On the other hand, little or no issue can be taken with the approach of using more than one drug in desperately ill patients, when the causative microorganism is not known.

What is less clear is how often one of the drugs given in combination interferes with the action of the other or others, a phenomenon defined as antagonism, or whether the drugs in combination exert a greater antibacterial effect than either one alone, in which case they are said to display synergism. Obviously, the former would constitute an important additional disadvantage attendant to the use of antimicrobial combinations, while the latter might be, in some instances, a subtle but definite benefit.

It is not difficult to show antagonism *in vitro* between drugs that affect primarily protein synthesis and that are bacteriostatic, such as tetracyclines and chloramphenicol, and agents that work primarily by disrupting bacterial cell wall synthesis and that are bactericidal, such as the penicillins and cephalosporins. However, it is much more difficult to document this phenomenon *in vivo,* either clinically or experimentally. For example, administration of tetracycline to rabbits with experimental Streptococcus viridans endocarditis failed to make infection in these animals more refractory to subsequent treatment with penicillin.[1] And while treatment of dogs with pneumococcal meningitis with administration of chloramphenicol before penicillin led to a diminution in bacterial killing in the cerebrospinal fluid when compared with penicillin given alone, antagonism was not demonstrable when the two drugs were given simultaneously or when penicillin was given before chloramphenicol.[2] Despite these equivocal results, bacterial meningitis is probably the only clinical situation in which bacterial antagonism enjoys some credibility. This stems largely from the findings of Lepper and Dowling[3] that patients with pneumococcal meningitis who were treated with a combination of aureomycin and penicillin had a significantly lower survival rate than those treated with penicillin alone. Obviously, this study has not and could not be repeated, and subsequent attempts to show differences in mortality in children with meningitis treated with ampicillin alone as opposed to the combination of ampicillin, chloramphenicol and streptomycin, showed only borderline differences in favor of the single drug.[4] Against this must be weighed the many thousands of children with childhood meningitis who have been successfully treated with a combination of two and three drugs, and the many patients in whom bacterial meningitis was inadvertently partially treated with bacteriostatic drugs followed by successful treatment with bactericidal agents without deleterious effects.[5] As a matter of fact, with the advent of some strains of ampicillin-resistant Hemophilus influenzae,[6] combination therapy of meningitis is back in vogue.

The bulk of the evidence, then, suggests that antibiotic antagonism is probably not clinically important. A better case, however, can be made for antibiotic synergism. A notable example is, of course, the use of two or more drugs in tuberculosis. Here the drug combination presumably confers its advantage by preventing or slowing the emergence of resistant tubercle bacilli. More pertinent to this discussion of synergism, however, is the ability of two drugs to be effective in a situation where neither works alone; the synergistic action of penicillin and an aminoglycoside against most enterococci is the most striking example. This is particularly important in endocarditis, in

which the drugs have to act in an environment in which host defenses are suboptimal. For example, surface phagocytosis probably does not occur in the relatively acellular vegetation.

In such a setting, it may also be useful to extend the definition of synergism to the concept that although one drug may be useful, the addition of a second agent may make the combination even more effective. It has been shown in experimental Streptococcus viridans endocarditis, for example, that the combination of penicillin G and streptomycin achieved cures more rapidly than penicillin alone[7] even though the infecting organism was exceedingly sensitive to penicillin. Translated to the clinical situation, this may mean that patients with Streptococcus viridans subacute bacterial endocarditis (SBE) treated with a combination of penicillin and streptomycin may require only two weeks of parenteral therapy, compared with the customary four-week course that is employed with penicillin. There is suggestive evidence that this is the case,[8] and if these observations are confirmed in a larger series of patients, the reduction in length of stay in hospital and its attendant costs would be significant.

It is, of course, tempting to extend these observations to other clinical situations in which host defenses have been compromised—such as a immunosuppressed, neutropenic host with malignant disease, who is so susceptible to infection particularly with Gram negative bacteria. However, here the data are equivocal. For example, a recent clinical trial indicated that the combination of cephalothin-carbenicillin-gentamicin was no better than cephalothin-carbenicillin given alone.[9] Before proposing that a combination of antimicrobials will act synergistically, three criteria should be fulfilled: (1) the drugs must show synergism against the putative pathogen *in vitro;* (2) if possible, synergism must be shown in an experimental infection akin to the infection in man, and (3) the combination must be tested in man in a controlled clinical trial. Within the constraints of these criteria, it seems useful to investigate combinations of drugs against those organisms that continue to pose a hazard of life-threatening infection. However, until synergism can be shown for a combination, the better part of valor is to use only those agents to which the organisms clearly have been shown to be sensitive. Moreover, where possible these drugs should be used singly rather than in combination. Finally, when combination agents are used they need to be deployed as single agents rather than as a single preparation in fixed combination.

ROBERT G. PETERSDORF, MD
Professor and Chairman
Department of Medicine
University of Washington
School of Medicine, Seattle

REFERENCES

1. Pelletier LL Jr, Petersdorf RG: Unpublished observations
2. Wallace JF, Smith RH, Garcia M, et al: Studies on the pathogenesis of meningitis—VI. Antagonism between penicillin and chloramphenicol in experimental pneumococcal meningitis. J Lab Clin Med 70:408-418, 1967
3. Lepper MH, Dowling HF: Treatment of pneumococcal meningitis with penicillin compared with penicillin plus aureomycin. Arch Intern Med 88:489-494, 1951
4. Mathies AW Jr, Leedom JM, Ivler D, et al: Antibiotic antagonism in bacterial meningitis. Antimicrob Agents Chemother pp 218-224, 1967
5. Harter DH: Preliminary antibiotic therapy and bacterial meningitis. Arch Neurol 9:343-347, 1963
6. Katz SL: Ampicillin-resistant hemophilus influenzae type B —A status report. Pediatrics 55:6-8, 1975
7. Durack DT, Pelletier LL Jr, Petersdorf RG: Chemotherapy of experimental streptococcal endocarditis—II. Synergism between penicillin and streptomycin against penicillin-sensitive streptococci. J Clin Invest 53:829-833, Mar 1974
8. Tan JS, Terhune CA Jr, Kaplan S, et al: Successful two-week treatment schedule for penicillin-susceptible streptococcus viridans endocarditis. Lancet 2:1340-1343, 1971
9. Klastersky J, Henry A, Hensgens C, et al: Gram-negative infections in cancer—Study of empiric therapy comparing carbenicillin-cephalothin with and without gentamicin. JAMA 227:45-48, Jan 1974

Editorial Essay

On the Withholding of Physicians' Services

FOR MORE than a decade practicing physicians have experienced a growing sense of frustration and with it growing resentment. Not only have there been mounting costs in patient care and clearly discriminatory cost controls against physicians, but worse, there has been increasing interference with medical practice by those who assume some authority but take no responsibility for what is or is not done for a patient who may be sick, injured or unable to cope for whatever reason. The root causes have been both economic and political.

First it was "third parties" in the private sector, and then government. Both have been guilty of discriminatory actions against physicians and both have built up large bureaucracies against whose medical practice decisions a practicing physician is virtually powerless—unless he wishes to invest a substantial amount of time and energy in making his case each time he differs with a bureaucratic decision. And most recently the

courts have decided to bring medical practice and medical practitioners to account under rules which may be appropriate enough for the legal system, but which affect medical practice and patient care adversely by making patients potential adversaries of their physicians. This fosters the development of wary doctor-patient relationships and the unwholesome practice of defensive medicine—which is always costly and seldom necessary or even best for the patient.

All of this has been frustrating, and as frustration mounts there is an understandable search for some force which can be brought to bear quickly and with effect. In our society, labor unions have developed such a force—though critics contend it has been done at some considerable cost to the freedom of their members and the public. The ultimate force that labor unions use is the strike, and to use this force effectively the union must be prepared to carry it on until the hurt it causes becomes intolerable to the employer, the public, or both. Unless this capability to hurt is real and there is willingness to use it, a strike method will not work.

The union idea has become attractive to many physicians in the same way it has been attractive to other groups of people who have been discriminated against or whose working conditions have been less than satisfactory. Further, those younger physicians, interns and residents in training, have shown that for them it can produce results. But it is worth remembering that, unlike most practicing physicians, interns and residents are in an employee status and also that their cause has had some emotional appeal to the public. They were serving the poor, they were television heroes, and their working conditions aroused sympathy. It is also worth noting that their protest was most effective when they did the opposite of withholding care—when they admitted everyone who needed care to the hospital and simply failed to discharge anyone. This was a quite different situation from that in which most practicing physicians now find themselves.

It seems to be becoming clear that the mass withholding of physicians' services is something to be feared by all concerned: profession, patients and general public. For the profession it flies in the face of the image and tradition of selfless service to the sick and injured. There is real danger that the profession will be viewed as self-serving at the expense of patients and the public. Physicians are not a deprived segment of society —often overworked, yes, but not deprived. There is usually no great public sympathy for the plight of physicians except as patients and patient care are affected, for better or worse. For an ill patient there is real fear: "Will my doctor be willing to help me when I need him?" or "Will I be able to get any care at all?" For the public there not only is this same kind of fear, but also the fear created by any strike that threatens the public safety, such as by a strike of the police or firemen. For reasons such as these it seems unlikely that a strike by physicians could have much public support for very long.

The recent experience in Northern California is perhaps worth noting. When the professional liability insurance premiums of some four thousand doctors were abruptly doubled or tripled this acutely affected several specialties including anesthesiology. All but a few anesthesiologists felt that they should not have to meet these costs and pass them on to their patients, and more or less in unison most withdrew their services. There was substantial support for their position from physicians in other specialties and in other as yet unaffected parts of the state. Initially the public sensed injustice and there was considerable public support for the doctors. But when a number of community hospitals began to be seriously hurt financially, and needed patient care was being deferred, and the California legislature indicated an intention to deal with the problem in the current session, there was an abrupt reversal of public support for the further withholding of services. The anesthesiologists wisely decided to return to work even though many of their number wanted to remain "out" until legislation satisfactory to them was indeed enacted. There could be lessons to be learned from this experience.

These are perilous days for medicine in this nation. In history, there have been times when physicians were slaves and other times when they were honored and respected leaders of the tribe. In whatever role, physicians have always been essential and have served in accordance with the will of society. While it is not likely that physicians will be actually enslaved in today's society, nevertheless it is true that the shackles of governmental controls are beginning to be felt by every practicing physician as they begin to restrict his freedom to exercise his best judgment in caring for his patients. And there is reason to believe that Congress may soon enact a law which will actually indenture young physicians for a period

of involuntary service. The trend is clearly toward greater public control both of physicians and the medicine they practice.

It is well to ask, then, does medicine have any real social, economic or political strength that it can bring to bear in these critical times—and if so where does it lie? It is certainly not at the ballot box. Physicians have only one vote in a thousand and legislators know this. It is not in the physicians' pocketbooks, although these have to be tapped to achieve a variety of professional goals. And it is clearly not in the profession's ability to cause suffering or hurt—or even unnecessary inconveniences—to the sick or injured. Rather the strength of medicine lies in the opposite of these. It lies in first earning and then mobilizing the vigorous support of patients and the general public for its goals. This can amount to an enormous power, far surpassing any power the profession can hope to generate within itself. It needs to be cultivated continually, in times of stress as well as in times less stressful, so that it can be brought to bear when needed.

These are times for the profession to keep its head—and for physicians to keep their cool. The role to be sought in society is that of wise and respected leadership, and the power to be mobilized is that of public understanding and support. The test for every action of every physician, of every group of physicians and of the profession itself is whether or not that action is best for patients and, therefore, for the public generally. It will always be true that what is best for patients is in the long run best for the medical profession. If the withholding of physicians' services can be justified by this test, then well and good. But there can be no doubt that the withholding of physicians' services can be a double-edged sword, and one edge could turn out to be quite a lot sharper than the other.

—MSMW

"Myasthenia Gravis"

Or the Autoimmunity, Thymic Disease, Neuromuscular Block Poser

MYASTHENIA GRAVIS is a disease that presents clinically with the symptoms of a postsynaptic neuromuscular block; the question arises—What causes this neuromuscular block? Two major clues loom large, thymic disease and autoimmunity; relating these to each other and to the neuromuscular deficit provides the poser of myasthenia gravis.

Thymic disease is consistently present in myasthenia gravis. In 15 percent of cases there is thymoma and in the remaining cases infiltration of thymus with lymphocytes and plasma cells and lymphoid germinal centers (these histological changes are also found in the nontumorous thymus adjacent to thymoma in myasthenia gravis). The nontumorous thymus in myasthenia gravis is, by common usage, termed hyperplastic but since the weight falls within the normal range this term is probably incorrect; the histological changes are more consistent with thymitis. The other important point to note with respect to the thymus in myasthenia gravis is that thymectomy, on an empirical basis, has been shown to cure or produce a substantial remission in up to 80 percent of cases. Failure to respond to thymectomy can be attributed in most cases to ectopic thymic tissue, incomplete thymectomy or irreversible neuromuscular damage with long-standing disease.

Autoimmunity was first suggested in myasthenia gravis in 1960 and since that time this concept has been amply substantiated. There is extensive serological evidence of antibodies to a variety of self antigens and other corroborative evidence, including clinical and serological overlap with other autoimmune diseases and a predominance of certain histocompatibility antigen types probably related to the presence of certain immune regulation genes. The real question seems to be not Is there an autoimmune reaction? but rather How does an autoimmune reaction cause neuromuscular block?

Direct blockade of transmission by autoantibodies to the acetylcholine receptor sites is the concept that most people would regard as implicit when autoimmunity is broached in myasthenia gravis. This pathogenesis is supported by the finding that immunization of animals with purified acetylcholine receptors from electric eels results in autoantibodies to endogenous acetylcholine receptors which cause a postsynaptic lesion in the recipient and also produce an acute curare-like neuromuscular block when applied to a neuromuscular preparation *in vitro*.[1,2] More recently, autoantibodies to acetylcholine receptor proteins have been detected in the serum of patients with

myasthenia gravis but these do *not* react with the acetylcholine binding site of the receptor[2] and an acute curare-like activity has *not* been convincingly shown in the serum of patients with myasthenia gravis.[3] Furthermore, a major deficiency of the concept of direct autoantibody blockade of neuromuscular transmission in myasthenia gravis is that it fails to account for thymic disease and the clear-cut ameliorative effects of thymectomy. Thymectomy does not produce a comparable amelioration of other autoimmune diseases such as systemic lupus erythematous or the autoimmune disease of New Zealand black (NZB) mice in which thymectomy not only fails to produce improvement but actually causes disease progression.

The alternative interpretation of the triad of autoimmunity, thymic disease and neuromuscular block is that an autoimmune reaction is directed towards the thymus, and that as a consequence of autoimmune disease of the thymus a neuromuscular blocking substance is released; this theory places the thymus in the line of causality and explains the special relationship of thymic disease and thymectomy in myasthenia gravis. Thymopoietin is a polypeptide hormone of the thymus that causes a neuromuscular block similar to that of myasthenia gravis, and was in fact isolated by this neuromuscular effect. Thymopoietin also induces the differentiation of bone marrow precursor cells (prothymocytes) to thymocytes and this is considered its physiological function. The complete 49 amino acid sequence of thymopoietin (M.W. 5562) has been determined and a 13 amino acid fragment has been synthesized that is biologically active in producing both thymocyte differentiation[4] and neuromuscular block.[5] Thymopoietin is released in experimental autoimmune thymitis so that from these studies the autoimmune reaction in myasthenia gravis would appear to be directed primarily towards the thymus and result in autoimmune thymitis, release of thymopoietin and neuromuscular block. The muscle autoantibodies found in myasthenia gravis, including the acetylcholine receptor antibody, are also cross-reactive with thymus[2] and could thus be regarded as antithymus antibodies and indicative of autoimmunity to thymus.

The mechanism by which thymopoietin causes neuromuscular block is of especial interest since thymopoietin does *not* simply compete for the acetylcholine receptor to produce a curare-like block. A single injection of as little as 4 ng thymopoietin per mouse causes a detectable neuromuscular deficit one to five days later. This suggests that thymopoietin is affecting a regulatory mechanism that inhibits the production of functional acetylcholine receptors, but does so with delayed kinetics that show a deficit after one to five days. It is envisaged that persistently elevated thymopoietin levels would result in chronic stimulation of this regulatory mechanism and cause the severe neuromuscular deficit that is found in myasthenia gravis. This delayed time-course for the appearance of thymopoietin-induced neuromuscular effects accounts for the seeming paradox in myasthenia gravis that whereas substantial evidence points to a circulating humoral substance produced by the thymus as a cause of the neuromuscular block, no acute curare-like activity can be detected in the thymus or in the serum of patients with myasthenia gravis; thymopoietin does produce a neuromuscular block but the kinetics of this are such that it would not be observed in the acute assays used to detect curare.

Finally, the answers to two questions would seem particularly pertinent to resolving completely the interrelationship of autoimmunity, thymic disease and neuromuscular block. First, if autoantibodies to acetylcholine receptors cause the neuromuscular block of myasthenia gravis, Can immunoglobulin molecules from myasthenic serum be shown to cause an acute curare-like effect *in vitro* on a neuromuscular preparation?—since this can be done with neuromuscular blocking autoantibodies generated experimentally. Second, if thymopoietin causes the neuromuscular block of myasthenia gravis, Can elevated levels of thymopoietin be detected in the serum?—using a sensitive technique such as radioimmunoassay. The answers to these questions should soon be available so, it is hoped, we will soon have a solution that will satisfy all for the autoimmunity, thymic disease, neuromuscular block poser of myasthenia gravis.

GIDEON GOLDSTEIN, MD, PH D
Memorial Sloan-Kettering Cancer Center
New York City

REFERENCES

1. Patrick J, Lindstrom JM, Culp B, et al: Studies on purified eel acetylcholine receptor and anti-acetylcholine receptor antibody. Proc Nat Acad Sci USA 70:3334-3338, Dec 1973

2. Lindstrom J, Lennon V, Seybold M, et al: Experimental autoimmune myasthenia gravis and myasthenia gravis: Biochemical and immunochemical aspects. Ann NY Acad Sci, in press

3. Goldstein G, Mackay IR: The Human Thymus. London, Heineman, 1969

4. Schlesinger DH, Goldstein G, Scheid MP, et al: Chemical synthesis of a peptide fragment of thymopoietin II that induces selective T-cell differentiation. Cell 5:367-370, Aug 1975

5. Goldstein G, Schlesinger DH: Thymopoietin and myasthenia gravis. Neostigmine-responsive neuromuscular block produced experimentally by a synthetic peptide fragment of thymopoietin. Lancet, in press

Continuing Medical Education in Community Hospitals

His own continuing education is, and always has been, an important responsibility for every physician during a lifetime of practice. It is important for the inner satisfaction of a conscientious physician and it is no less important for the welfare of his patients. In recent years the rapid progress of medical science—a result of unprecedented public support for medical research—has focused not only professional but public attention upon the continuing education of practicing physicians. It has become necessary for this to become more visible and more measurable.

The medical profession has responded with programs at the national and state levels, and formal programs giving visible and measurable credit for time and effort in continuing medical education are growing rapidly. Accompanying this growth has been a decentralization of the authority to offer the essential Category I credit, first to medical schools, then to state medical associations and specialty societies which wish to become accredited. And now in California and the West this authority and responsibility is being further decentralized to community hospitals which can qualify for approval by the accredited state medical association.

This has the advantage of bringing approved programs of continuing medical education to the hospitals where physicians practice and where their educational needs can be more readily identified. But it also brings problems when the resources of a hospital and its medical staff are insufficient to conduct their own program without help from outside.

Elsewhere in this issue of the Journal, Alvin Block describes experience with this problem in a community hospital and gives some helpful advice for others. But it is becoming increasingly clear that more attention should be given to linking the educational resources of the profession more closely to the educational needs of physicians in practice, and it is also increasingly clear that if this is to be done the necessary financial resources will have to be found.

—MSMW

CASE REPORTS

Refer to: Caro XJ, Sutherland PW, Mitchell DB, et al: Traumatic hemoglobinuria associated with conga drumming. West J Med 123:141-144, Aug 1975

Traumatic Hemoglobinuria Associated with Conga Drumming

XAVIER J. CARO, MD
PAUL W. SUTHERLAND, MD
DACE B. MITCHELL, MD
FREDERIC S. GLAZENER, MD
San Francisco

SINCE THE FIRST DESCRIPTION by Fleischer in 1881[1] several cases of march hemoglobinuria have been reported. A causal relationship between running on hard surfaces and hemoglobinuria was suggested by Attlee,[2] but it was Davidson[3] who showed that hemolysis was caused by mechanical trauma to circulating erythrocytes in the plantar blood vessels. This simple explanation has been confirmed by Buckle[4] and Spicer;[5] no cellular defect has been isolated. Traumatic hemoglobinuria involving the upper extremities has been encountered less commonly than march hemoglobinuria. In 1903 Ensor and Barratt[6] reported hemoglobinuria in a demented patient who was accustomed to violent bouts of head slapping. More recently, hemoglobinuria has been shown to occur after karate exercises[7] and after conga drum playing.[8]

We report here three persons in whom traumatic hemoglobinuria occurred after conga drumming. Schistocytosis was also present in one, and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in another.

From the Department of Medicine, University of California, San Francisco, School of Medicine.

Submitted March 6, 1975.

Reprint requests to: X. J. Caro, MD, Editorial Office, 994-M, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

Reports of Cases

CASE 1. A 31-year-old black man, a college student, was seen at the University of California Ambulatory and Community Medicine Clinic because of episodic passing of dark urine. Four weeks earlier he had enrolled in a conga drumming class, and since then he had noted cola-colored urine after each strenuous, bare-handed drumming session. The urine returned to normal color within a few hours. He reported using only an oral decongestant compound (Allerest®) occasionally and marijuana infrequently.

On physical examination, the patient was found to be healthy-appearing and muscular, with normal vital signs. The palmar surfaces of the hands were normal, there was no hepatosplenomegaly and posture was normal. Findings in the remainder of the examination were unremarkable.

A sample of urine that the patient brought with him was qualitatively strongly positive for protein and hemoglobin (Labstix) and appeared black. Findings on analysis of a fresh urine specimen, hematocrit determination and a blood smear were within normal limits, but the reticulocyte count was 3.5 percent. A leukocyte count and differential count, erythrocyte sedimentation rate (Westergren), serological test for syphilis (Venereal Disease Research Laboratories—VDRL—reaction), liver function tests and determinations of blood urea nitrogen, serum protein and albumin, and total and direct bilirubin gave findings within normal limits. Serum creatinine was 1.3 mg per 100 ml (normal up to 1.2 mg per 100 ml), creatinine clearance was normal at 144 ml per minute and plasma hemoglobin was less than 5 mg per 100 ml (normal). Results of hemoglobin electrophoresis, direct and indirect Coombs' tests, Hams' test, glucose-water test and porphyrin screen of urine were negative or normal. Glucose-6-phosphate dehydrogenase was 1 international unit (IU) per gram of hemoglobin (normal 4 to 8 IU). Findings on a chest x-ray study and an intravenous pyelogram were unremarkable. There was no growth on urine culture. On examination of stool, Giardia lamblia cysts were noted.

The giardiasis was treated with metronidazole (Flagyl), 200 mg three times daily for one week.

The patient was informed of the probable reason for the hemoglobinuria and was advised to maintain a high intake of fluids at each drumming session.

CASE 2. A healthy 32-year-old black man, a medical student, had recently noted dark brown urine after conga drumming sessions. He was a conga drummer of 17 years' experience and had played professionally. Approximately six months previously he noted dark brown urine 30 minutes after a drumming session and again two hours later. Though he sensed a fullness in both flanks for two days after the session, findings on urinalysis on the first day were reported to be normal by a college physician. Since then the patient has noticed dark urine three times, always after strenuous drumming sessions. In the recent past he had participated actively in swimming and karate (without board-breaking exercises), but no dark urine had been noted. He used no medications or street drugs.

On physical examination, the patient's vital signs were normal. Flat feet, tinea pedis and an associated palmar id reaction were noted. The palmar surfaces were otherwise normal. There was no enlargement of abdominal organs, and posture was normal. The remainder of the physical examination was not remarkable. Findings on analysis of a fresh urine specimen, hematocrit determination, blood smear, leukocyte count and differential count were within normal limits. Reticulocyte count was 1.9 percent. A VDRL reaction test and determinations of blood urea nitrogen, serum creatinine, serum protein and albumin, and total and direct bilirubin gave either negative or normal findings, as did hemoglobin electrophoresis, a direct and indirect Coombs' test, a Hams' test, a glucose-water test and a glucose-6-phosphate dehydrogenase determination. No abnormalities were noted on an x-ray film of the chest.

CASE 3. A healthy 29-year-old black man, an acquaintance of the patient in Case 2, had occasionally noticed dark urine after particularly strenuous drumming sessions. He was an amateur conga drummer of 17 years' experience. He could not recall when he first passed dark urine in association with drumming, but was sure that it was always after his "heaviest jam sessions." Because he had recently experienced such an episode, he agreed to take part in the drumming session (described below) but declined any blood tests other than those described. He occasionally used marijuana, lysergic acid diethylamide and amphetamine sulfate.

On examination, vital signs and posture were found to be normal. There was no enlargement of abdominal organs. The palmar surfaces were normal, and the remainder of the physical examination was unremarkable. The hematocrit determination, blood smear and reticulocyte count gave findings within normal limits. Results of a leukocyte count and differential count, a sickle-cell screen and a glucose-6-phosphate dehydrogenase determination were negative or normal.

Materials and Methods

Drumming Session

A drumming session was arranged for the three subjects in order to carefully investigate the hemoglobinuria. At the time of this session it had been six months, one month and two weeks respectively since Patients 1, 2 and 3 had first been seen. Hemoglobinuria had abated in Patient 1 during this time and now occurred only after long, strenuous sessions. All three had refrained from drumming for five to seven days and none had had any medications for a week before the session.

Blood was withdrawn from an antecubital vein and transferred to plain and ethylenediamine tetraacetic acid (EDTA) treated containers, and urine specimens were collected before and after the drumming session. Patients 1 and 3 played in their accustomed sitting positions, whereas Patient 2 stood. All drums were of standard conga styling; the playing surface of each was thick animal skin cured to wood-hard consistency. The drums rested on a carpeted floor and were held in place by metal stands. Each patient had fluids as he desired during the drumming session. The session lasted for 2½ hours and consisted of 20-minute drumming periods alternated with 10-minute rests.

Laboratory Methods

Serum hemoglobin levels were measured by the benzidine-peroxidase method,[9] serum haptoglobins by the Beckman microzone technique,[10] and serum creatine phosphokinase and lactic dehydrogenase by the kinetic rate method.[11,12]

After concentration by ultrafiltration in collodion bags, urine specimens were qualitatively studied by starch gel electrophoresis.[9] Rough quantitation of urine hemoglobin was provided by use of a commercially produced test (Hemastix). Protein was quantitated by the sulfosalicylic

acid method and was graded from 0 to + + + +. A Prussian blue stain was used to test for the presence of hemosiderin. Phenotyping of serum haptoglobin before and after the session was done by starch gel electrophoresis in Tris/citrate-borate discontinuous buffer at pH 8.65.[9] Hematologic review was made of peripheral blood smears prepared with Wright's stain.

Results

In Patient 1, baseline values were normal except for slightly depressed serum haptoglobin (42 mg per 100 ml) (Table 1). Baseline serum haptoglobin in Patient 2 was elevated (181 mg per 100 ml) as was creatine phosphokinase (74 IU). In Patient 3, laboratory values were normal. Patients 2 and 3 had haptoglobin of type 2-1; Patient 1's phenotype was not determined.

The drumming session was without incident, and the three subjects felt well but tired afterwards. Patients 1 and 2 noticed a tingling sensation in their hands; both had associated this in the past with the voiding of dark urine. Urine samples collected immediately after the drumming session showed the expected changes of mild hemoglobinuria (Table 1).

The urine specimens from Patients 2 and 3 contained a wide spectrum of proteins. The heme protein in each had a greater anodal migration than normal hemoglobin A, and it was believed to represent hemoglobin Koellicker.[13] A fainter band with the migration pattern of hemoglobin A was also present in each. Myoglobin was not present in either sample. Urine concentration was not done on the specimen from Patient 1, but hemoglobin was determined by positive benzidine staining after differential precipitation with ammonium sulfate.[9] After drumming, serum hemoglobin increased by 29, 136 and 124 mg per 100 ml, and serum haptoglobin decreased by 91, 90 and 24 mg per 100 ml in Patients 1, 2 and 3, respectively. Serum creatine phosphokinase rose in Patients 1 and 3 and remained slightly elevated in Patient 2. Serum lactic dehydrogenase became abnormal only in Patient 2.

Discussion

As in other patients with traumatic hemoglobinuria, elevated serum hemoglobin and depressed serum haptoglobin were present in these patients after traumatic exercise. In two of them there was grossly pigmented urine and in all there was labo-

TABLE 1.—*Alterations in Plasma and Urine after Conga Drumming for 2½ Hours*

Substance	*Normal Value*	*Patient 1*		*Patient 2*		*Patient 3*	
		Before	*After*	*Before*	*After*	*Before*	*After*
Plasma							
Hemoglobin (mg/100 ml)	0.5-25	7.08	36.6	13.5	149.9	9.9	134
Haptoglobin (mg/100 ml)	50-150	42	33	181	91	103	79
Creatine phosphokinase (IU/liter)	10-62	60	88	74	70	60	140
Lactic dehydrogenase (IU/liter)	20-95	82	75	70	135	90	65
Urine							
Color	..	Clear yellow	Clear yellow	Clear yellow	Cloudy brown	Clear yellow	Pink
Specific gravity	..	1.012	1.008	1.018	1.023	1.007	1.004
Albumin*	None	None	Trace	None	+ + +	None	+ +
Hemoglobin*	None	None	+ +	None	+ + + +	None	+ + + +
Leukocytes (per high power field)	None	0-2	1-3	2-10	5-10	0-2	0-3
Erythrocytes (per high power field)	None	None	0-1	None	None	None	0-2
Casts (per high power field)	None	None	0-2 granular	None	Many granular	None	Many granular
Hemosiderin	None	None	None	None	None	None	None

*Graded from 0 to + + + +.

ratory evidence of hemoglobinuria. A rise in serum creatine phosphokinase suggested there might be a component of muscle injury in at least two of the subjects, because creatine phosphokinase levels are said not to be affected by hemolysis,[9] and were not elevated in a patient with traumatic hemoglobinuria caused by running.[5] In none of our patients was there demonstrable myoglobinuria. The finding of granular casts is consistent with previous reports of this condition.

It is postulated[4,5,14] that the trauma described in these patients, when added to the pummeling and deformation to which a red cell is normally subjected,[15] is sufficient to cause damage to or total destruction of a small quantity of erythrocytes. It has been estimated that this hemolysis represents only 6 to 40 ml of whole blood.[5,16,17] The resultant free hemoglobin is dissociated into alpha and beta dimers and is bound to the $alpha_2$ globulin, haptoglobin, thus preventing the urinary loss of hemoglobin. If the haptoglobin reserve is overwhelmed by the total serum hemoglobin or, perhaps, by the rapidity of the rise in serum hemoglobin, hemoglobinuria results. Hemosiderinuria may also occur,[18] as may methemalbuminuria.[19,20] We did not find either in our patients.

Although poikilocytosis and "four-leaf-clover" cells have been described in a patient,[21] schistocytosis is not a usual part of traumatic hemoglobinuria. Trace schistocytosis was seen in Patient 2; helmet cells were occasionally seen. The role of glucose-6-phosphate dehydrogenase deficiency, if any, in this disorder is unclear. This deficiency is known to increase susceptibility to hemolysis when affected persons are treated with certain drugs or during intercurrent illnesses.[22] It is not known if there is an increased tendency toward traumatic hemolysis under the conditions described here.

Perhaps the frequency and the potential seriousness of traumatic hemoglobinuria ought to be reappraised. Two-thirds of 26 runners in the 1941 Boston Marathon showed an increase in plasma hemoglobin, and four had hemoglobinuria.[23] In Kaden's report of hemoglobinuria in a conga drummer he stated that other members of the patient's drumming group had noted similar episodes in association with prolonged and violent playing.[8] Our Patient 2 reported he knew of six other cases of pigmenturia associated with conga drumming among his friends. Because of the renewed interest in hand drumming, this problem may be encountered more often in the future. A recent report by Pollard and Weiss,[24] which describes a patient who developed acute tubular necrosis with traumatic hemoglobinuria after a marathon race, emphasizes the potential seriousness of this condition. For this reason there should be an increased awareness of this phenomenon.

Summary

Traumatic hemoglobinuria associated with conga drumming in three young black men was documented during a monitored 2½-hour drumming session. Hemoglobinuria, a mean 10-fold rise in serum hemoglobin values and a mean 38 percent fall in serum haptoglobin were seen after this drumming session. Unexpected and new findings included a glucose-6-phosphate dehydrogenase (G-6-PD) deficiency in one subject and trace schistocytosis in another.

REFERENCES

1. Fleischer R: II. Aus der medicinischen Klinik zu Erlangen: Ueber eine neue Form von Haemoglobinurie beim Menschen. Klin Wochenschr 47:691-694, 1881

2. Attlee WHW: Haemoglobinuria following exertion. Lancet 1: 1400, 1937

3. Davidson RJL: Exertional haemoglobinuria—A report on three cases with studies on the haemolytic mechanism. J Clin Pathol 17:536-540, 1964

4. Buckle RM: Exertional (march) haemoglobinuria—Reduction of haemolytic episodes by use of sorbo-rubber insoles in shoes. Lancet 1:1137-1138, 1965

5. Spicer AJ: Studies on march haemoglobinuria. Br Med J 1:115-156, 1970

6. Ensor CW, Barratt JOW: Paroxysmal haemoglobinuria of traumatic origin. Med Chir Trans 86:165-195, 1903

7. Streeton JA: Traumatic haemoglobinuria caused by karate exercises. Lancet 2:191-192, 1967

8. Kaden WS: Traumatic haemoglobinuria in conga-drum players. Lancet 1:1341-1342, 1970

9. Frankel S, Reitman S, Sonnenwirth AC (Eds): Gradwohl's Clinical Laboratory Methods and Diagnosis—A Textbook on Laboratory Procedures and Their Interpretation, 7th Ed. St. Louis, C V Mosby, 1970

10. Colfs B, Verheyden J: A rapid method for the determination of serum haptoglobin. Clin Chim Acta 12:470-472, 1965

11. Rosalki SB: An improved procedure for serum creatine phosphokinase determination. J Lab Clin Med 69:696-705, 1967

12. Wacker WEC, Ulmer DD, Vallee BL: Metalloenzymes and myocardial infarction. N Engl J Med 255:449-456, 1956

13. Marti HR, Beale D, Lehmann H: Haemoglobin Koelliker—A new acquired haemoglobin appearing after severe haemolysis: α_2 minus 141 Arg β_2. Acta Haematol 37:174-180, 1967

14. Streeton JA: March haemoglobinuria. Br Med J 1:567, 1970

15. Jandl JH: Symposium on disorders of the red cell—The pathophysiology of hemolytic anemias: A forward. Am J Med 41:657-665, 1966

16. Gilligan DR, Altschule MD: March hemoglobinuria in a woman. N Engl J Med 243:944-948, 1950

17. Gilligan DR, Blumgart HL: March hemoglobinuria—Studies of the clinical characteristics, blood metabolism and mechanism: With observations on three new cases, and review of the literature. Medicine (Baltimore) 20:341-395, 1941

18. White P: Degradation of hemoglobin, *In* Williams WJ, Beutler E, Erslev AJ, et al (Eds): Hematology. New York, McGraw-Hill Book Company, 1972, pp 191-197

19. Fairley NH: Methaemalbumin (pseudo-methaemoglobin). Nature (Lond) 142:1156-1157, 1938

20. Shinowara GY, Walters MI: Hematin—Studies on protein complexes and determination in human plasma. Am J Clin Pathol 40:113-122, 1963

21. Watson EM, Fischer LC: Paroxysmal "march" haemoglobinuria—With a report of a case. Am J Clin Pathol 5:151-158, 1935

22. Carson PE, Frischer H: Glucose-6-phosphate dehydrogenase deficiency and related disorders of the pentose phosphate pathway. Am J Med 41:744-761, 1966

23. Gilligan DR, Altschule MD, Katersky EM: Physiological intravascular hemolysis of exercise—Hemoglobinemia and hemoglobinuria following cross-country runs. J Clin Invest 22:859-869, 1943

24. Pollard TD, Weiss IW: Acute tubular necrosis in a patient with march hemoglobinuria. N Engl J Med 283:803-804, 1970

LETTERS *to the Editor*

Registry for Liver Tumors Associated with Oral Contraceptives

To the Editor: We have discovered a substantial number of cases of liver tumors associated with oral contraceptives. These cases have been documented elsewhere and we are publishing our report in *Obstetrics and Gynecology*. We are establishing a registry for these cases and are presently researching methods for early identification of patients at risk. The registry will be staffed by a nationally known gastroenterologist, hepatologist, pathologist and surgeon. We will serve as codirectors and will coordinate the various disciplines through our department of Obstetrics and Gynecology.

Case reports are invited for the Registry for Liver Tumors Associated with Oral Contraceptives. Full acknowledgment will be accorded. Either of us may be contacted at the Orange County Medical Center, University of California, Irvine, Department of Gynecology and Obstetrics. Telephone (714) 633-9393 Ext. 183.

Edward D. Nissen, MD
Deryck R. Kent, MD
Irvine, California

NPR's for Medicare

To the Editor: A convalescent hospital "nonphysician representative (NPR)" for Medicare has decreed that a diabetic with hypertensive heart disease, myocardial infarct just 14 days ago, complicated by congestive heart failure and pneumonia, sometimes requiring oxygen administration for survival, no longer needs "skilled nursing care."

I must confess, I don't know whether I am angrier at the apparent fiscal expediency of just letting die a person I believe to have some quality of life left, or whether I am angrier at the abbrogation of my authority by nurses who prostitute their profession. This is a widespread problem I don't see solved by our usual administrative measures as likely as by public indignation over bureaucratic oppression. My patient chose me, the physician, to decide whether a "skilled nurse" was needed to observe her need for oxygen, etc.—not a nurse-turned-bureaucrat whose future money and power often conflict with the patient's best interest.

How can I fulfill my responsibilities when a nurse can overrule my authority?

Howard F. Long, MD, MPH
Pleasanton, CA

Soap Photodermatitis

To the Editor: In his Epitome of Progress entitled "Soap Photodermatitis" (West J Med 121: 314, Oct 1974), Dr. J. B. Pace (Graduate Division, Department of Family Medicine, University of California, Irvine) stated that Proctor & Gamble's Zest® toilet bar contains brominated salicylanilides. The statement is incorrect. A highly purified form of tribromsalan (3,4′5-tribromosalicylanilide) formerly was used in Zest; however, its use was discontinued in October, 1972. Zest, therefore, has contained no brominated salicylanilide for over two and one-half years. Data from controlled diagnostic tests with Zest which have been performed under our sponsorship by private physicians also fail to support the statement that Zest commonly induces photosensitization.

We continue to be interested in assisting physicians to determine if cutaneous reactions they see are, in fact, adverse reactions to our products, or if they merely are coincidental to their use. To that end, physicians who believe they have adverse reactions to Zest are encouraged to contact me.

James E. Weaver, PH D
Biological Research Services
The Procter & Gamble Company
11520 Reed Hartman Highway
Cincinnati, OH 45241

Fluoridation

To the Editor: Your editorial comment in the May issue written by Professor Newbrun, "Water Fluoridation and Dietary Fluoride Ingestion" [122:437-442, May 1975], is so full of inaccuracies, that it can not remain unchallenged. Such inaccurate and biased reporting is not worthy of your excellent journal.

Professor Newbrun emphasizes *concentration* of fluoride, and regrets that Dr. Lee has confused *dosage* with *concentration*. I believe Professor Newbrun is the one who is confused. Dosage is the *only* measurement used in pharmacology, except for topical application; concentration is used only in *toxicology*. All orally or parenterally administered substances for the prevention or treatment of illness, including those also occurring in nature, are measured in grams (solids), cc (liquids) or units (those substances which can be standardized only biologically). I know of no exceptions. If concentration *is* used, it is *always* qualified by a definite amount. "20 cc of a 10 percent solution" obviously means the same as 2 grams. Even toxicology prefers to use dosage whenever possible (the fatal dose of substance A is B grams, not C percent or D ppm). Concentration is limited to circumstances, where dosage-measurements cannot be carried out, such as chemical contaminants in air or water, including purposely added contaminants.

It is indeed true, that data on dietary fluoride ingestion are sparse and unreliable. That should be reason to stress research in that field, before adding additional fluoride.

All the studies on children about presence or absence of toxic side effects in fluoridated and nonfluoridated areas were probably well intended. But they have two faults, which make them totally irrelevant: (a) None of the studies was double-blind; (b) Such a study tries to obscure the fact that fluoridated water is consumed by everybody in any age, not only by children. The studies should have been carried out on *old* people, who have consumed fluoridated water for a lifetime. In old people the findings might have been different.

Alternate methods to fluoridation are much better than Professor Newbrun wants us to believe. Table 3 in his article, page 439 (Cost and Efficacy of Fluorides in Various Forms) is based on the author's imagination and desires. There are no controlled studies comparing different methods of administration. Fluoride tablets or drops are indeed administered only once a day, but there is no study showing that this is inferior. Frequent administration is desirable only where high *blood-levels* have to be maintained. *Tissue* absorption of ingested fluoride is spotty anyway, as shown by the fact that in fluorosis the teeth are mottled rather than uniformly discolored. Besides, we do have the technology to put fluoride in slow-release form. The notion that with fluoridated water the teeth are bathed in fluoride repeatedly during the day is also misleading. Fluoridated water contains 1/10,000 percent of fluoride, while fluoride solutions used for topical treatment contain 1 percent fluoride. Fluoridated water has no topical effect whatever, regardless of the length of time or frequency it is in contact with the teeth. Even the cost has been misstated. I do not know the actual cost of water fluoridation, but the cost of fluoride tablets or drops should have been listed as "zero to $4.00." Most children take vitamin pills or drops anyway, and the vitamins with fluoride cost the same as without; the additional fluoride is free. Even taking fluoride pills alone, the cost to the public is less than $4.00 per year. I priced several leading pharmacies, not chain-pharmacies. If Professor Newbrun cannot obtain the fluoride at this price, I will be happy to furnish it to him and still make a handsome profit.

I hope that you will print this letter in a spirit of fairness.

Max Schlachter, MD
Oakland

* * *

To the Editor: Advocates of fluoridation of public water supplies may well succeed in their effort to impose this treatment on every citizen. But those of us free of that arrogance which assures us that we know what's best for everyone else still take umbrage at statements such as Dr. Lee's. In his article in the issue of May 1975 entitled "Optimal Fluoridation" [Lee JR: Optimal fluoridation—The concept and its application to municipal fluoridation. West J Med 122:431-436, May 1975], he mentions enforcement of fluoridation "by the process of majority vote, itself a technique quite curious and unique among public health affairs."

This "technique" of course reflects the poorly articulated realization that fluoridation is not and never has been a public health measure. Dental caries may be of great public concern, but is not

communicable and poses no serious threat to the well-being of society. There is *no role* for the use of police power in enforcing fluoridation or compelling its use by fluoridating public water supplies. The only curious thing is that in a nation nominally devoted to the protection of rights of the minority, forcible medication of the public for noncommunicable disease should ever have been allowed even with a vote.

MATTHEW L. HOWARD, MD
Ukiah, CA

* * *

TO THE EDITOR: In his rebuttal of Dr. Lee [Newbrun E: Water fluoridation and dietary fluoride ingestion—Editoral comment. West J Med 122: 437-442, May 1975], Dr. Newbrun used flawed statistical procedures. Newbrun cites a mortality table for San Francisco, 1951 to 1973, showing the rates per thousand from 11.8 to 12.4. Several are incorrect, as they are lower than in the official annual reports for San Francisco.

Newbrun omits the fourteen years, 1955 through 1968. Two of these are 13.3, one is 13.2, three are 13.1, one is 13.0, two are 12.9, one is 12.7, two are 12.6, one is 12.4 and one is 12.0. These figures might be significantly high, but significance levels can not be set, because of the many other factors operating. In order to assure the harmlessness of fluoridation, the table is clearly irrelevant and without experimental and statistical merit.

Similarly without merit is the study of 32 so-called pairs of cities which were cited. They were in no sense paired, except in having equal numbers of residents. The variations in death rates were enormous, and in opposite directions from pair to pair. Taking a grand average was invalid, and merely served to confuse the picture. The data were for only one year in some pairs, and two years in the others.

The mortality tables do not prove harmlessness, but if compared cities show, for example, greater cancer incidence with fluoride, then extensive unbiased controlled experiments with individuals are urgently indicated.

In this letter, some of the inadequacies of the article have been mentioned. An enumeration of all flaws in the Newbrun paper is too lengthly for inclusion.

HUBERT A. ARNOLD, PH D
Associate Professor
Department of Mathematics
University of California, Davis

Trauma Rounds

Chief Discussants
MICHAEL H. HUMPHREYS, MD
GEORGE SHELDON, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Humphreys MH, Sheldon G: Acute renal failure in trauma patients (Trauma Rounds). West J Med 123: 148-153, Aug 1975

Acute Renal Failure in Trauma Patients

WILLIAM COPELAND, MD:* A 28-year-old man was admitted to the emergency room in profound shock with two stab wounds in the abdomen. The patient had been found in Golden Gate Park and it is not known at what time he was injured. Examination showed the patient to be unresponsive with poor peripheral perfusion. Blood pressure was unobtainable and the pulse was 120 beats per minute and thready. After immediate resuscitation with three liters of Ringer's acetate, blood pressure became palpable at 90 mm of mercury and the pulse was 110 beats per minute.

There were two stab wounds each 1 cm in length in close proximity to the umbilicus in the left lower quadrant. The patient's vital signs deteriorated again and he was promptly taken to surgery. On exploratory laparotomy, 2 liters of free blood was noted in the peritoneal cavity and injuries were seen to consist of multiple penetrating wounds of the small bowel and a single, 1 cm laceration of the infrarenal aorta.

The aorta was repaired by lateral suture and the small bowel injuries were closed with a single layer technique. During operation and in the postoperative period there was no urine output. By the fourth postoperative day serum creatinine was 7.6 and potassium was 6.1. Hemodialysis was instituted and discontinued on the 24th postinjury day following return of renal function.

In the postoperative period the patient gave a history of having stabbed himself with a pair of scissors and it was estimated that he had been in the park for at least 8 hours.

GEORGE SHELDON, MD:† We have presented this case today because the statement has recently been made that acute renal failure is no longer a problem in trauma patients. This patient sustained renal failure because of prolonged untreated shock. Renal dialysis has indeed proved to be an effective means of supporting patients with acute renal failure. Its use is not without its problems, however. Dr. Michael Humphreys has reviewed our experience with acute renal failure at San Francisco General Hospital and will review the indications for dialysis and describe current methods of management.

MICHAEL HUMPHREYS, MD:‡ We have reviewed our experience with dialysis for acute renal failure in the past 21 months. A total of 85 patients was seen during this time with a clinical diagnosis of acute renal failure. In 38 of these patients, either peritoneal or hemodialysis related to the

*Intern, Trauma Service, San Francisco General Hospital.

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

Reprint requests to: D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco, CA 94110.

†Chief, Trauma Service, San Francisco General Hospital.

‡Chief, Renal Dialysis Center, University of California at San Francisco General Hospital.

renal failure was required. Eleven patients had dialysis because of renal failure developing in the setting of trauma; there was massive trauma in 8 of these, and in the other 3 renal failure developed related to myoglobinuria from ischemia injury to an extremity. Six of the eight patients with massive trauma died, but all of the patients with myoglobinuria and ischemia injury survived, so that mortality for all 11 patients was 55 percent. These patients as a group averaged 12 hemodialyses per patient before renal function recovered or death occurred.

With this as background, it may be useful to talk for a minute about the pathogenesis and differential diagnosis of acute renal failure. Oliguria, the most common manifestation of acute renal failure, can be defined as urine output which is less than 500 ml per day in an average adult. As to functional assessment, it is a rate of urine output which is insufficient to permit excretion of the daily load of solute delivered to the circulation from body metabolism; any rate of urine flow which results in a solute accumulation in the body can be defined as oliguria. Therefore, the differentiation between oliguric and nonoliguric renal failure is a semantic one, although nonoliguric renal failure appears to be more benign and carries a better prognosis. The initial clinical insult, whether severe shock, sepsis or massive trauma, initiates a series of events which results in inadequate renal perfusion either as a result of compromise of the systemic circulation or due to changes in the blood itself. The effects of renal ischemia are manifest in a variety of ways, from mild renal dysfunction reflected as mild azotemia to severe renal damage which requires extensive supportive therapy.

The primary problem that the clinician faces when impaired renal function develops in association with oliguria is to differentiate between prerenal and renal azotemia. Table 1 shows the criteria which are used to differentiate between these two groups. In both forms of renal failure the urine output is decreased and there is solute accumulation in the blood. With prerenal azotemia, tubular function is intact and urine osmolality is usually higher than plasma osmolality. If the ratio of urine-to-plasma osmolality is 1.5 or greater, then the renal insufficiency may well be prerenal in origin. The kidneys perceive this situation as pronounced volume depletion, and react by trying to conserve sodium; the result is that urine sodium concentration will be less than 20 mEq per liter and often less than 10 mEq per liter. Urine potassium will be high, reflecting hyperaldosteronism. In prerenal azotemia the urine-to-plasma ratio for creatinine concentration is greater than 14 to 1. The urine sediment may be relatively benign, only a few granular casts being seen. If the problem is renal parenchymal failure, there is oliguria but the urine-to-plasma osmolality ratio approaches one, the urine sodium concentration is greater than 20 mEq per liter and the urine potassium concentration is low. The ratio of urine-to-plasma creatinine is also low, and the urine sediment may contain larger number of epithelial cells.

None of these diagnostic indices is absolute; in fact, values from patients with prerenal azotemia may overlap with those from patients with established acute tubular necrosis. This was well illustrated in a study by Handa and Morrin (Canad. Med. Assoc. J. 96:78-82, 1967). They reviewed the values of diagnostic indices in 10 patients with acute tubular necrosis compared with 13 patients with functional renal failure (prerenal azotemia). Neither the urine sodium concentration nor the urine-to-plasma creatinine ratio alone provided very complete separation of the two groups of patients. However, when these indices were combined by dividing the urine sodium by the urine-to-plasma creatinine ratio, near-perfect separation occurred. All patients with acute tubular necrosis had values of this fraction above 2, while all but

TABLE 1.—*Diagnostic Indices in Oliguric Acute Renal Failure*

	Pre-Renal Azotemia	*Parenchymal Renal Damage (Acute Tubular Necrosis)*
Urine Volume	<500 ml/24°	<500 ml/24°
Urine Osmolality	>400 mOsm/kg (U/P_{osm}>1.5)	±300 mOsm/kg (U/P_{osm}±1)
Urine Sodium	<10 mEq/l	>20 mEq/l
Urine Potassium	>50 mEq/l	<40 mEq/l
Urine-to-plasma creatinine	>14	<14
Urine Sediment	Benign; hyaline and granular casts	Epithelial cells and epithelial cell casts

one patient with functional renal failure had a value less than 1.3. These results have subsequently been confirmed by other investigators, and they showed the importance of early urine measurements in patients with oliguria and rising levels of blood urea nitrogen (BUN) and creatinine. When these measurements are used properly, accurate diagnosis of the cause of the oliguria can be made in most cases.

One of the standard means of treating a patient with oliguric acute renal failure has been by mannitol diuresis. This is still generally accepted as being of benefit in preventing renal failure although its effectiveness has not been unequivocally proven. Mannitol is confined to the extracellular space. An intravenous bolus injection expands the vascular compartment, increases the cardiac output, decreases renal vasoconstriction and improves renal blood flow, thereby improving renal function and urine output.

DR. SHELDON: *How do you determine whether mannitol is going to work?*

DR. HUMPHREYS: A patient in whom there is evidence of prerenal azotemia is most apt to respond and this can be defined using the tests I previously described. However, it is our feeling that any patient who has renal failure of recent onset should receive an infusion of mannitol, on the chance that urine flow may increase regardless of what the indices show. One ampule containing 12.5 grams of mannitol is administered intravenously over a period of 10 minutes or so. If the cardiovascular system is not compromised, usually there will be an increase in urine flow to some 50 ml an hour for the next four hours. If the response is less, we usually repeat the injection, and if there is no response accept the fact that acute renal failure is established.

The potent diuretic furosemide has been used in an effort to produce diuresis in patients with oliguric acute renal failure. However, there is no evidence that administration of furosemide is of any benefit in preventing renal failure. Moreover, there is now experimental evidence suggesting that the converse may be true and that this drug may actually aggravate the renal problem by worsening any preexisting hypovolemia. Another aspect of the problem is that the diagnostic features are confused by the administration of a diuretic. Following administration of furosemide, even though the patient remains oliguric, the effect on the renal tubule is such that urine sodium concentration will increase. The ability to assess the nature of the renal failure is thus impaired. So I would like to emphasize that diuretics should be avoided because they are not therapeutic and can compound the problem of making a diagnosis as to the cause of the oliguria.

In a relatively large percentage of patients seen in our hospital, myoglobinuria-related renal failure due to extensive muscle damage is present. The tip-off to this diagnosis involves examination of the urine. Myoglobin produces a urine which is red-brown in color and which gives a positive test for blood. However, results of testing the urine sediment are negative for red blood cells. The usual laboratory test for myoglobin is relatively crude and a negative finding on a laboratory test for myoglobin does not necessarily rule it out. Correlated with the findings of abnormally colored urine is the determination that the normal BUN-to-creatinine ratio in plasma of 10:1 no longer exists. In patients with myoglobinuria due to muscle damage, the serum creatinine rises more rapidly than the BUN, so the ratio is less than 10:1. This reflects a release of creatinine phosphate from the damaged muscle. Usually results of other tests of muscle damage, such as of the enzymes creatine phosphokinase (CPK) and serum glutamic oxaloacetic transaminase (SGOT), show elevated levels.

The treatment of myoglobinuria consists of a cocktail which we use in an effort to prevent the renal failure from becoming established. It is composed of a liter of 5 percent dextrose and water solution from which 200 ml have been removed and two ampules of sodium bicarbonate and two ampules of mannitol have been added. This reconstituted liter contains 100 mEq of sodium bicarbonate plus 25 grams of mannitol. The sodium bicarbonate helps to alkalinize the urine and maintain myoglobin solubility, the mannitol and water restore vascular volume and enhance renal perfusion. One liter of this is given at the rate of 250 ml per hour over a period of four hours. If there is a response, judged by urine output, administration of the cocktail is continued at a rate equal to the urine output. If at the end of four hours, there is no response to the cocktail, then the assumption has to be made that renal parenchymal damage is present and the patient's condition will not respond to further trials.

In every patient with acute renal failure, careful monitoring of fluid balance is indicated. Intake, output and daily weights should be recorded;

these should include estimates of the increased insensible losses due to fever and wounds. Phosphate retention is a result of renal failure, and can be treated by administration of oral antacids which are phosphate binders. Rarely, calcium supplements may be indicated; serum calcium levels should be measured several times weekly.

Another aspect of treatment is to avoid administering compounds containing magnesium because magnesium levels can rise to alarming levels in patients with renal failure. In addition, administration of drugs that have renal toxicity such as some of the antibiotics like kanamycin or those that are excreted by the kidney must be avoided, since toxic blood levels may result. Acidosis can be treated with sodium bicarbonate administration. Vigorous treatment of infection is indicated because sepsis is associated with the potential for further damage to the kidney. Although these patients become anemic, transfusions are not necessarily needed. The hematocrit usually stabilizes in the low 20's and this is perfectly adequate for oxygen transport. Patients in the diuretic phase of recovery from renal failure should be watched carefully since shifts in fluids and electrolytes can be profound, and all the previous considerations must be kept in mind.

DR. SHELDON: *Dr. Humphreys, would you discuss the indications for hemodialysis or for peritoneal dialysis?*

DR. HUMPHREYS: The chief indications for the institution of dialysis are hyperkalemia (serum potassium > 7 mEq per liter), heart failure from fluid overload, severe metabolic acidosis and, in general, a rise in BUN above 120 and creatinine above 10—although the numbers by themselves rarely dictate when dialysis should commence. Other indications for dialysis consist of toxic or uremic complications such as pericarditis, nausea and vomiting, bleeding, seizures or coma.

One question often asked is: When do you select hemodialysis as opposed to peritoneal dialysis? Obviously, the answer relates to what is available—not all hospitals having facilities for acute hemodialysis. If only one or two dialyses may be required, peritoneal dialysis may be the method of choice. The best patients for peritoneal dialysis are those in whom rates of catabolism are low.

Hemodialysis should be the method of treatment for rapidly deteriorating patients and those who will in all probability require repeated dialysis. The absolute indications for hemodialysis are rapid catabolism—particularly in patients with burns, major trauma or severe crushing injuries—or recent abdominal surgical operation which would contraindicate introduction of a peritoneal catheter. Finally, the removal of toxins and poisons is a situation in which peritoneal dialysis is relatively ineffective and hemodialysis is preferred.

Relative contraindications to hemodialysis are systemic hypotension or limited myocardial reserve, as blood flow through the artificial kidney may be poor. Since anticoagulation must be carried out while dialysis is being done, those patients who have severe bleeding problems present formidable difficulties for hemodialysis. In the patients in whom systemic anticoagulation is contraindicated—such as patients with head trauma—regional heparinization can be used and may permit dialysis without greatly risking bleeding complications.

Some of the complications associated with hemodialysis are bleeding and rapid changes in blood volume which can result in shock and hypotension. Abrupt shifts in fluid balance and electrolyte concentrations can produce cardiac arrhythmias. Although the dialyzing membrane may rupture, blood loss is usually not a major problem, as current machines limit this potential. Occasionally, due to technical errors, the composition of the dialysate may be such that hemolysis results. A final complication which can arise is the dialysis disequilibrium syndrome. When high levels of BUN and creatinine are lowered abruptly during dialysis, a syndrome may develop characterized by central nervous system abnormalities, such as headache, nausea, vomiting, coma, seizures and occasionally even death. The mechanism for this syndrome is unknown, but may be related to the rapid removal of solutes from the spinal fluid, resulting in cerebral edema. In order to avoid this complication we make the first dialysis a short one to minimize unduly rapid solute removal.

DR. SHELDON: The incidence of renal failure in trauma patients is approximately equal to the incidence of the respiratory distress syndrome of shock and trauma. When we make vigorous attempts to avoid pulmonary failure by restricting fluids we may inadvertantly trade this for renal failure. Since our mortality rate for renal failure

as documented by Dr. Humphreys is between 55 and 75 percent and our mortality rate in those patients who develop severe respiratory failure is approximately 20 percent, treatment directed toward preventing renal failure is well advised even though respiratory problems may be aggravated.

In patients with renal failure, one goal of treatment should be to cut back on the catabolic nature of the injury so that the muscle breakdown is lessened. The problem relates to the fact that when muscle breaks down, the products of this breakdown cannot be excreted. Attempts to nourish these patients are limited by the need to limit fluids. Measure of catabolism in battle casualties shows the faster the rise in BUN levels, the greater the catabolic rate. Almost all of the nitrogen in nitrogen balance studies is excreted in urine. In the acute post-trauma period, muscle rather than fat breaks down preferentially to supply nutritional needs. It has been shown that in dogs in which kidneys have been removed, increases in BUN levels occur quickly. If amino acids and hypertonic glucose are administered, the rate of rise of BUN levels can be slowed by about 50 percent. The primary problem related to protein administration is the need to limit fluids. If too much fluid is administered, dialysis may be required to get rid of extra fluid.

During the initial catabolic phase following trauma, a patient may lose 10 grams of nitrogen a day. During the recovery or anabolic period, the return to normal is much slower than in the initial catabolic phase, and takes approximately three times as long. We advise that parenteral nutrition using an amino acid mix be started immediately after renal failure is recognized. Concentrated solutions of dextrose are administered simultaneously to cut down on the nitrogen loss. It requires approximately 4,000 calories to cut off protein catabolism and to establish positive nitrogen balance. If we were able to cut off catabolism, the urea rise would decrease and it is possible actually to put muscle mass back into the patient.

In a study at Massachusetts General Hospital, with patients in acute tubular necrosis (ATN) treated in double blind fashion, gross survivals were better in the group treated with hyperalimentation. Although their dialysis needs were lessened only slightly, their nutritional status was improved and this was probably the factor which increased survival.

J. ENGLEBERT DUNPHY, MD:* I concur based on a personal experience in battle casualties sent to us for treatment of renal failure. The prognosis was dismal in these patients in whom renal failure developed after trauma. In most there were associated sepsis, major trauma and wound complications. These survival rates have not seemed to change much over the years despite the enthusiasm for dialysis.

LAWRENCE WAY, MD:† *Dr. Humphreys, what is the best mechanism for handling the nutritional status of a patient in renal failure? Do you agree with Dr. Sheldon's recommendations?*

DR. HUMPHREYS: I am a convert to Dr. Sheldon's program. Within the restraints of fluid balance, attempts should be made to establish caloric balance in these patients. I believe this will shorten the time on dialysis and provide a better nutritional reserve. We do not need to be concerned with limiting the protein intake and can let these patients take as much protein as they can handle. We are concerned about fluid and potassium loads, however, and fluid and electrolyte balance should be monitored carefully.

F. WILLIAM BLAISDELL, MD:‡ I would like to reemphasize that the mortality from renal failure is higher than that for respiratory failure. From a clinical point of view, when dealing with trauma patients a fall in renal output within the first 24 hours following a critical clinical insult is due to inadequate renal perfusion from one of two factors—hypovolemia or cardiac failure. If the venous pressure is low to normal, a fluid load is indicated until renal output is established, or central venous pressure rises above normal. If necessary, I do not mind putting a patient in pulmonary edema, for under this circumstance I know where I am. Acute water-load pulmonary edema is relatively easily treated and readily reversible. If central venous pressure rises or pulmonary edema ensues without establishing good renal output, then attention directed toward improving cardiac function is warranted.

Once we have a patient in a stable environment such as the intensive care unit, the use of a Swan-Ganz catheter in these critical situations will permit careful titration of vascular volume and cardiac functions. A pulmonary wedge pressure in

*Chairman, Department of Surgery, University of California San Francisco Medical Center.

†Associate Professor of Surgery, University of California San Francisco Medical Center.

‡Chief, Surgical Service, San Francisco General Hospital.

excess of 10 to 15 mm of mercury with no urine output directs attention toward cardiac resuscitation. A low wedge pressure is an indication for more volume. Once the initial 24 hour period has passed, the lack of response to these measures suggests the possibility of renal damage. At this point we have time to obtain consultation and apply the sophisticated tests Dr. Humphreys advocated to differentiate between prerenal failure due to inadequate circulation and renal tubular damage. I believe that most of the 11 cases of renal failure which developed in our trauma population were preventable had adequate volume been administered early and had volume therapy been maintained at optimal levels.

Dr. Humphreys: Dr. Blaisdell touched on the issue of pulmonary as opposed to renal consequences of hydration—a point over which the Nephrology Service gets into disagreement with our medical respiratory unit very frequently. Rather than get too far into the controversy, I will say that this has to be decided in each individual case. However, in most instances we would agree with the point that volume is needed in these patients to improve renal function. I have seen a number of cases in which there is a general overall capillary leak syndrome; under these situations, the volume titration with the Swan-Ganz catheter is essential. In most of these patients, there are vascular volumes which when measured are found to be on the low side, and therefore volume replacement is needed.

Dr. Blaisdell: We might conclude from the discussion that attempts to straddle the fence between pulmonary failure on one hand and renal failure on the other may result in inadequate volume resuscitation and may result in the worst outcome of all: a combination of respiratory and renal failure which in our experience has a 70 to 95 percent fatality.

Refer to: Block AL: Continuing medical education in small community hospitals (Medical Education). West J Med 123: 154-158, Aug 1975

Continuing Medical Education in Small Community Hospitals

ALVIN L. BLOCK, MD, *Napa, California*

For a number of years, the need for medical audit and the desirability of building a program of continuing medical education (CME) to be based on deficiencies disclosed by audit has been stressed. However, even though these two areas of activity are interrelated, the techniques required in the planning and implementation of each of them is very different indeed. To date, even though continuing medical education is the more important of the two for physicians, much more attention has been devoted to audit—in terms of theory, in literature and in meetings. (In California alone, twelve California Medical Association-California Hospital Association workshop conferences were planned in 1974 and twelve have been scheduled for the first half of 1975. This does not include sessions arranged by the Joint Commission on Accreditation of Hospitals, numbering at least nine from June 1974 to February 1975.) Perhaps it has been assumed that once a need for improvement has been identified and defined, the educational programs needed to fill that need will spring into existence de novo; if so, that type of thinking is in error.

Of course, the nature and management of the educational problem will vary greatly, depending on what sort of hospital and staff one deals with. For those institutions whose major function is academic and whose purpose includes teaching, training and research in addition to patient care, much of the capability for creating such teaching programs is already present as a part of the institution's daily activity. For a small community hospital whose efforts are almost totally consumed by primary patient care, the practical aspects of beginning and sustaining a CME program are very different and have received scant attention.

This paper is an effort to describe some of the major questions generated by the efforts of a small community hospital staff in creating its educational program and some of our answers to those questions. It is intended as a kind of practical guide to "how do you get it started?" for a community hospital with limited educational funds and no full time teaching personnel. The program and principles described have now been employed in our own 135-bed hospital for almost two years and are for the most part results of the lessons learned from numerous false starts. Since most of the hospitals in California have 150 beds or less,[1] it is precisely in this area that we must succeed with continuing medical education if it is to have the impact upon the profession that is expected and desired. The difficulties encountered by most smaller community hospitals are usually a direct outgrowth of the character of the hospital and its staff, meaning (1) small size of hospital with meager financial and physical resources available for the creation and maintenance of these programs, and (2) staff comprised totally of private practicing physicians with resulting limitations in time for the planning and administration of CME programs. The medical staff and hospital engaged in planning these programs encounter almost immediately several types of problems which must be dealt with before any further work can proceed. For example:

Reprint requests to: A. L. Block, MD, Valley Medical Clinic, 3230 Beard Road, Napa, CA 94558.

CME Coordinator

Who will coordinate the program, including details such as writing letters to speakers, contracting for films and arranging for slide projectors?

CME Topics

How does one choose the topics for CME sessions?

CME Programs

How and where can one obtain suitable speakers?

What audiovisual materials are available and where can they be obtained?

How can physician attendance and participation be encouraged?

What is the general cost of supporting a CME program in this setting?

Although this list is by no means exhaustive, it provides a sampling of some central questions which must be answered in order to construct programs of this type.

Coordinator

At the start, a major obstacle is finding some person whose schedule will allow time to coordinate educational programs and attend to the details preliminary to any successful, organized educational endeavor. Such details include setting dates, writing letters, arranging for teaching aids, reserving lunches, providing publicity and other similar small—but important and time-consuming—activities. In most instances, a physician would best fill this position by virtue of his medical background, his sensitivity to the needs and desires of fellow physicians and his ability to exchange ideas freely with them almost daily about this subject.

If such a person is available, well and good. However, in the private practice community, the prospects of locating somebody with this interest and the sort of leisure which would permit him to undertake these duties in addition to those already imposed on him by a busy practice is fairly remote. Time becomes the limiting factor, and in the midst of a day crowded with seeing patients, noon hours filled with telephone calls and insurance forms, and evenings scheduled for meetings of various kinds, only rarely is such a person available as a volunteer.

Assigning these responsibilities to an education committee usually is not the answer. Generally it results in an inadequate program because the factors that make it difficult for the private practice community to initiate and promulgate a CME program in the first place are not substantially altered. It fails to shift the burden away from the already overburdened practitioner of medicine, but instead creates another meeting to attend, worsening his time deficit further. Also, under the committee approach, there often is a failure to delegate responsibility specifically, which dilutes authority and breeds inaction and discontinuity.

Since, in our own experience, voluntary efforts proved to be inadequate, our hospital and staff found it expedient to hire a medical coordinator, part of whose task it has become to do those things mentioned above. His responsibilities in a small hospital may well include some in fields other than education—such as audit activities, Professional Standards Review Organization (PSRO) criteria and work related to hospital-provided services (coronary care and intensive care units, inhalation therapy, electrocardiographic facilities, dialysis). But included in his activities and responsibilities is the creation, initiation and maintenance of the CME program for the members of the medical staff. In many instances, he should find it useful to attend most or all department audit meetings and department business meetings in a continuing effort to be close to staff physicians and know their appraisal of their educational needs and their assessment of the CME program's usefulness.

A part-time coordinator may be all that is required. In this way, choosing a practicing physician for the position has the advantages of assuring that the coordinator is alert to the thinking of the private practice community, while not fractionating the staff into hospital-based versus private practice physicians.

Topics

The topics, the form and the manner of presentation used in CME efforts are determined in large measure by the educational needs of the staff, as well as by the resources available for dealing with these needs.

At present, the approach most often used in defining educational needs is first to discover deficiencies, using audit activities in the hospital, and then to base CME programs on their correction. To the degree that the audit is sensitive enough to detect and define true deficiencies in patient care, this principle has merit. But it is fallacious to assume that audit is the only good

determinant of educational direction. Many times the interest of the staff in a given area of education or the personal experience of members of the staff about problem areas within the hospital will serve as an excellent index of educational usefulness. I have on occasion found that the observations made by one perceptive physician serve as well as an extensive audit in determining a worthwhile educational effort. Though audit is valuable as a guide to education, slavish adherence to audit is inappropriate and may lead to omission of worthy suggestions.

Whatever programs are created, they will require enough flexibility to focus on the problems unique to that particular staff. In our own hospital, we have formulated and now use the following broad format for our educational activities: (1) guest lecturers, (2) audiovisual aids and (3) small specialty and subspecialty gatherings.

Programs

Guest Lecturers

Since programs using guest lecturers require more effort in preparation and take more time for presentation, they are offered no more than twice monthly and are designed to appeal to broad segments of our staff. They deal often with topics of basic physiology and basic science (fluid and electrolyte reviews, principles of antibiotic use).

Speakers can be obtained in a number of ways. One excellent method is that of establishing a working arrangement with the chairman of the department of postgraduate education in one or two major teaching institutions (who can make available to you a pool of speakers with expertise in various subjects). Other good sources of lecturers are volunteer health organizations (heart associations and cancer societies) and pharmaceutical companies. However, in my experience these are less useful in supplying speakers on a specific topic.

When areas of deficiency have been identified (by whatever means) and when a topic and date have been decided upon, a letter can be sent from the medical coordinator to the university or assisting organization requesting a speaker for *that particular topic*. Since these are major programs for smaller community hospitals (speakers cost approximately $125), at least 90 minutes should be allotted for them and care should be taken in scheduling times. We have found the hours of 12:30 to 2 pm to be useful because many of our staff are in the hospital at this time.

Other points, suggested by our experience, may contribute to the success of programs:

- Consider an informal conference, perhaps with sandwich lunches, which allows the staff to eat and ask questions while the speaker talks.
- Pay close attention to a schedule; discipline yourself to begin and end when the announced schedule calls for it. The staff quickly becomes discouraged by meetings which drag on indeterminantly, extending into and eroding the afternoon office hours.
- Be certain that you have clearly defined in earlier preliminary correspondence with the speaker the precise areas of need and interest for your staff. He is at a distinct disadvantage if he does not know the desires and capabilities of your staff. Lectures which miss the mark are terribly destructive of future attendance and can be avoided by definite guidance and direction from the medical coordinator.
- Plan a meeting well in advance (one to two months) and publicize it as much as possible. Some techniques which have proved useful for us include having a large bulletin board conspicuously situated in a main hospital corridor, placing smaller bulletin boards at strategic locations (medical records, surgery lounge), publishing a monthly calendar that lists and describes activities for the coming month and even sending notices to the physicians' secretaries at their office with a request that the doctor's schedule be planned so as to permit his attendance at the CME meeting.

Audiovisual Aid Programs

A number of different techniques for programs are available, including videotapes, movies, audiotapes and a combination of tapes and slides. Of these, I have found videotapes and movies of most value and they will be discussed below in more detail.

Audiotapes are not new; they are presently being offered by many organizations[2-4] and cover a wide range of subjects. They have been widely used for years by many members of the medical profession, but in my personal experience they have more application and effectiveness in individual learning than in group or staff educational programs.

Slide programs with written or taped commentary are also available.[5-10] We have used them in a

limited way and have found them to be very useful in specific instances (for example, if the medical department wants a general review of ophthalmology as it applies to primary physicians). However, because their cost is $65 to $75 per program, their use for us has been restricted. Some programed material on professional education is available[7] but its relevance for our staff has been limited and its acceptance has proved to be poor.

Video cassettes and movies are a major source of teaching material for us, designed to appeal to smaller groups and discrete areas of need. Our particular hospital arrangement includes a conference room in which many of our staff eat lunch and which can easily be adapted for a movie or video cassette showing, allowing a presentation during the lunch hour.

Video cassettes are short (20 to 40 minutes long), can be found on a wide variety of subjects enabling one to select them according to a specific need and require a minimal effort to show (using a projector or video screen). They do, however, require that the medical coordinator put the program together well in advance—making the selection from the appropriate catalog, placing the order six to eight weeks beforehand, and scheduling the showing on the calendar. Last but certainly of considerable importance is the fact that video cassettes can be obtained cheaply (see below). Of course, their use requires a video screen. Several different models of these screens are currently marketed, ranging in price from $1,700 to $2,500. My experience in this field is not wide, but it would appear that as long as a video screen will handle ¾-inch tapes, there is little substantial difference among them.[11] This piece of equipment is important and will in the future constitute an increasingly important capability by means of which much of our educational material will be presented.

Tapes can be obtained from two major sources: commercial groups[12-16] and government.[17,18] Although commercial video cassettes frequently are excellent presentations, they have the distinct disadvantage of being expensive and, perhaps worse, are sometimes difficult to tailor to staff needs. If you subscribe to a commercial video cassette service, you take what their offering provdes—and while at times this covers some staff needs, at other times the program may interest only one or two members. Many financial arrangements are available, including rental (approximately $75 per tape for two weeks), sale ($150 per tape) or subscription ($500 to $700 per year for twice monthly programs).

The federal government is a gold mine of inexpensive video cassettes and movies.[17,18] These can be ordered through National Audiovisual Center and Brooke Army Medical Center, both of which publish extensive catalogs. The movies are acquired on loan at no cost while video cassettes can be obtained for $10 by having them tape from one of their master tapes onto a blank tape you send to them. Taping from master tapes affords an opportunity to build up a pool of ten to fifteen hours of cassettes, using a wide variety of master tapes on subjects of particular interest or need to your staff. The cost is minimal. Additionally, the cassettes provide a valuable reservoir of selected educational material which is readily available should a scheduled meeting or film showing be cancelled.

Many other sources for movies are available.[19,20] All arrange for educational films on request and at virtually no cost to the ordering hospital—a feature of paramount importance to a small community hospital with a limited educational budget. However, cassettes have provided us more flexibility than movies since the cassette remains ours until we choose to send it back for retaping, whereas movies have a definite prescheduled showing date and must be returned immediately afterwards. A word of caution regarding both video cassettes and movies: both can vary widely in the quality and manner of presentation. The catalog description and assessment can be very misleading. It is, therefore, advisable when possible to preview them before showing, allowing enough time for a substitute if they should prove to be unsatisfactory.

Specialty Meetings

A third continuing educational activity is using small conferences designed to appeal to specific needs of small groups within the staff (neuroradiology and neuropathology sessions, isotope meetings, coronary care unit conferences). At our hospital, the topics for presentation and discussion have, as a rule, been chosen primarily from material selected by the group concerned as suitable and interesting (as opposed to audit program selection). The number attending is frequently limited, perhaps four to six people.

It is surprising to see how often these conferences are sparked by one or two interested physicians who find time to review cases, select

pertinent x-ray films and slides, and generally prepare for the conference. Nonetheless, a medical coordinator can be very helpful by arranging to have slides made and films available, and generally by taking care of those administrative activities which would otherwise consume the time of the physicians handling the meeting. The principles of adequate notice and attention to strict time limitations noted earlier pertain here. Additionally, providing coffee and rolls can sometimes make early morning meetings more attractive.

In conclusion, I have discussed some of the immediate and practical problems encountered in the effort to generate a continuing medical education program, relating them specifically to a small community hospital in which all, or virtually all, of the medical staff are full-time, private practicing physicians. In so doing, I have described our particular format for continuing education, designed to satisfy differing educational needs within our medical staff. Included were: (1) formal lectures presenting basic material of interest and concern to most segments of a diversified staff, (2) audiovisual material intended to fill smaller, discrete needs of certain segments of our staff and (3) brief subspecialty meetings proposed to deal with very precise, isolated areas of interest for small segments of the staff. Our agenda calls each month for one or two outside speakers, four to five video cassette showings or movies and four to five subspecialty sessions. Our budget for this program is $1,000 to $1,200 per year.

Some principles found to be helpful in implementing all of these have included the following:

- Find a person who is interested in continuing medical education activity to initiate and pursue the mechanical, time-consuming administrative activity necessary for beginning and supervising these programs. If no one with enough time can be found, think seriously about paying somebody enough to enable him to take the time for such a project.
- Give explicit guidance to guest speakers as to subject material.
- Begin and end meetings with close attention to a schedule.
- Plan meetings well in advance and advertise them well, using bulletin boards, monthly calendars and word of mouth.
- Use breakfast and luncheon meetings as much as possible.
- Even though deficiencies indicated by audit are an important foundation for continuing education activity, draw freely and readily upon the experience and expressed desires of members of your staff as an equally vital source of educational programs.

REFERENCES

1. Hospitals in the United States, *In* American Hospital Association Guide to The Health Care Field—1974 Edition. Chicago, American Hospital Association, 1974, pp 35-53
2. Audio-Digest Foundation (CMA)
   1250 So. Glendale Ave.
   Glendale, CA 91205
3. Division of Continuing Education
   University of Pittsburgh
   School of Medicine
   Pittsburgh, PA 15261
4. The American College of Cardiology
   9650 Rockville Pike
   Bethesda, MD 20014
5. ROCOM
   1 Sunset Avenue
   Montclair, NJ 07042
6. Abbott Laboratories
   P.O. Box 352
   North Chicago, IL 60064
7. Ciba Foundation
   Ciba Pharmaceutical Company
   P.O. Box 1340
   Newark, NJ 07101
8. Med-Com Slide Lectures
   Med-Com Inc.
   2 Hammarskjold Plaza
   New York, NY 10017
9. Research Media Co.
   4 Midland Ave.
   Hicksville, NY 11801
10. Nuclear Associates, Inc.
    35 Urban Ave.
    Westburg, NJ 11590
11. Videotape, a revolution in the making. Mod Med 41:28-33, Dec 10, 1973
12. The Network for Continuing Medical Education
    15 Columbus Circle
    New York, NY 10023
13. McGraw Hill
    Institute for Continuing Physician Education
    1221 Ave. of the Americas
    New York, NY 10020
14. Video Digest
    660 S. Bonnie Brae
    Los Angeles, CA 90057
15. American Academy of Family Physicians
    1748 West 92nd Street
    Kansas City, MO 64114
16. Coordinator, Educational TV
    University of California, San Francisco
    San Francisco, CA 94143
17. National Audiovisual Center
    Washington, DC 20409
18. BAMC-TV Television Videotape Catalog
    Television Division
    Brooke Army Medical Center
    Fort Sam Houston, TX 78234
19. AMA, Medical Health Film Library
    535 N. Dearbon St.
    Chicago, IL 60610
20. Ayerst Association-Sterling Films
    2221 S. Olive
    Los Angeles, CA 90007

Clinical Note

Refer to: Mohler JG: Blood gases (Clinical Note). West J Med 123:159, Aug 1975

Blood Gases

JOHN G. MOHLER, MD, *Los Angeles*

MEASUREMENTS OF BLOOD GASES and hydrogen ion concentration (pH) have developed in most hospitals without a parallel development of training and quality control. While the growth of blood gas services has been exceedingly rapid, little has been done to ensure that machines meet standards of accuracy and reliability, especially for partial pressure of oxygen (Po_2). The manufacturers have not had to prove the same assurance of reliability as even the simplest new drug, even though most have tried hard, no rigorous standards exist. The results of the analysis can appear deceivingly accurate, yet can be dangerously incorrect; the cost of error and machine dissatisfaction is borne by the patient in dollars and well-being.

We have operated a quality control program in Los Angeles for more than one year. Iced blood samples with known values are delivered directly to subscribers at nominal cost. As a result, we have learned several important facts about blood gas machines as they function in the community and of those who use them. First, we have found that better trained people, whether in pulmonary laboratories or clinical chemistry, operate the less automatic machines and get the most reliable results by a considerable margin. We have also found that those automated machines made for small hospitals are, in fact, most prone to subtle error. In our study, the IL-313 type of machine averages more than 10 mm of mercury, and sometimes 20 mm of mercury, higher than the true value for blood Po_2. Our initial limited testing of the ABL-1 type of machine with known blood Po_2 values suggests it also needs sophisticated supervision. The Po_2 is higher than our values by 5 mm of mercury over a wide range. While this machine calibrates itself with liquid, it is not entirely clear that the liquid is the entire explanation for this difference. On the other hand, the nonautomatic models (113 and 213 of IL) read well within the required ± 2 mm of mercury tolerance on the average. Corning Model 165 reads slightly greater than tolerance;[1,2] Radiometer BMS-2 and 3 are within tolerance. All machines average to tolerance for carbon dioxide pressure (Pco_2) and pH.

We have concluded that the smarter the machine, the smarter must be the people who run it. Do not expect to replace well-trained pulmonary technicians or analysts, and proper supervision, by elaborate electronics without first acquiring the necessary biomedical engineers and the supervision required.

We suggest that instead of automation, half the money should be spent for straightforward nonautomatic machines and the other half on training operators. Quality control begins with well-trained analysts. Next, tonometer blood at Po_2 ranges from 40 to 80 mm of mercury or exchange iced blood samples regularly with other units. Agreement to ± 4 mm of mercury for Po_2 and Pco_2 is barely acceptable; larger differences must be explained. Do not expect much agreement at first. The magnitude of the disagreement, in fact, may be startling. Continued checking one with another results in surprising reliability if the differences are honestly resolved.

Quality control includes the director of the blood gas laboratory. This physician must review blood gas results for aberrant or impossible results. Patient breathing sea level room air, the sum of the arterial Po_2 and Pco_2 cannot be greater than 150 mm of mercury; the Po_2 value is very doubtful if the sum is greater than 140 mm of mercury. Sums are lower at higher altitudes. A sum less than 80 mm of mercury suggests, but does not prove, the sample is venous blood. The pulmonary specialist managing a blood gas laboratory is in the best position to note values inconsistent with the patient's problem. As he adds his interpretation of blood gas values, he also comes to know the clinical situation as well.

Finally, responsibility for quality control rests with the clinician who uses arterial blood gas results. He should particularly be skeptical of "machine numbers" as well as such interpretations. Inconsistency between results and his evaluation of his patient must be explained. This might take another arterial blood sample, or an education.

Reprint requests to: J. G. Mohler, MD, Director, Pulmonary Physiology Laboratories, Department of Hospitals, Los Angeles County/USC Medical Center, 1200 North State Street, Los Angeles, CA 90033.

REFERENCES

1. Mohler JG: Devices for blood gas analysis. N Engl J Med 290:632-633, Mar 14, 1974
2. Runck AH: Proper technic in measurement of blood gases. N Engl J Med 291:476, Aug 29, 1974

Refer to: Schofferman J, Yamauchi T: Overdose—The early treatment (Medical Information). West J Med 123:160-163, Aug 1975

Overdose—The Early Treatment

JEROME SCHOFFERMAN, MD, *and*
TERRY YAMAUCHI, MD, *Torrance, California*

THE ACCIDENTAL or purposeful ingestion of large quantities of drugs is epidemic.[1] Emergent care of an overdosed patient cannot be solely the responsibility of the emergency department physician, for in order for treatment to be most effective, it must be rendered early. Therefore, all physicians must be prepared to deliver immediate care for this potentially lethal condition. Unfortunately, although the basic goals of therapy are simple, many physicians are unfamiliar with the details of treatment. Much of what many of us have learned is based on anecdotes, and perhaps the scientific principles of therapy have not been adequately stressed. In addition, many of the reviews of the treatment of drug ingestion are quite general, making detailed information difficult to acquire.[2,3] With these thoughts in mind, we have attempted to provide concise, practical information for the early care of overdosed patients. Much of the body of data reviewed is based on studies *in vitro,* in animal models or in children, but the recommendations are quite applicable to adults. We will not attempt to describe long-term therapy, but will focus only on immediate care.

General Approach

The approach to an overdosed patient is divided into: (1) rapid evaluation, (2) critical support, (3) minimization of absorption and (4) general or specific therapy. The emphasis will vary depending on the presentation. A patient who walks into an office or emergency department able to relate the history of having taken an excess quantity of drugs, and in whom vital signs and mental status are normal, usually presents little problem initially. The emphasis is to minimize drug absorption as quickly as possible. However, care of a patient with central nervous system depression, hypotension or depressed respirations must have different emphasis. As in any critically ill patient, attention is directed toward maintenance of adequate airway, support of respiration and correction of hypotension. Only then can the physician turn to further evaluation and treatment.

Rapid Evaluation

When a stuporous or comatose patient is first seen, certain guidelines must be kept in mind. Because the history may be unreliable, one should not assume the patient is simply an overdose victim. Finding empty bottles at home, a history of suicide attempts or a history of depression may suggest overdose, but should not lull the physician into a false sense of diagnostic security. Even when a definite history of ingestion is available, other conditions such as hypoglycemia, head trauma or infection may be superimposed. Therefore, after obtaining a blood sample for a glucose determination, a bolus of 50 percent solution of dextrose should be given intravenously, and a rapid but careful physical examination should follow.

Certain physical signs are helpful when evaluating a possible overdose patient with an abnormal mental status. Small pupils may be seen in overdose of propoxyphene, organophosphate insecticides or narcotics. Therefore, if needle marks or miotic pupils are noted, 0.4 to 0.8 mg of naloxone IV should be administered to an adult and 5 to 10 micrograms (μg) per kg of body weight to a child. This drug is free of agonist properties and its use entails little or no risk. Overdoses of heroin, narcotic analgesics, pentazocine and possibly propoxyphene may be expected to respond within 1 to 2 minutes.[4] Dilated pupils as a specific sign are less useful, but may be a clue to ingestion of glutethimide, atropine, scopolamine amphetamines, cocaine or tricyclic antidepressants. Breath should be examined for the characteristic pungent odor of ethchlorvinol, alcohol, acetone or a fetor hepaticus. The head should be searched for bleeding, Battle's sign, "racoon eyes," cerebrospinal fluid leakage from nose or ears or other evidence of trauma. One should look for focal neurological findings which are unusual in uncomplicated overdose and should suggest an intracranial lesion. Nuchal rigidity might indicate sub-

From the Receiving-Emergency Division of the Departments of Medicine and Pediatrics, University of California, Los Angeles, School of Medicine, Harbor General Hospital, Torrance.

Submitted, revised, December 23, 1974.

Reprint requests to: J. Schofferman, MD, Receiving-Emergency Department, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

arachnoid hemorrhage or meningitis. Swelling of the limbs or pronounced muscle tenderness could be due to rhabdomyolysis with a possible compartment syndrome and may herald peripheral ischemia, neuropathy, hyperkalemia or myoglobinuria.

Certain laboratory data can be useful in evaluating possible drug overdose patients. Even with scant physical findings, an x-ray film of the chest may show pulmonary edema. Tests of arterial blood gases might show profound hypoxia due to pulmonary diseases or hypoventilation and unsuspected acid-base derangements may be detected. Findings on an electrocardiogram may show supraventricular or ventricular arrhythmias or even heart block of various degree.

Minimizing Absorption

After a patient has been stabilized and evaluated, attention must turn to minimizing further absorption of the toxin from the gastrointestinal tract. The following techniques are available: (1) evacuation of the stomach by emesis or aspiration-lavage, (2) adsorption of toxin by activated charcoal or (3) evacuation of the gastrointestinal tract with purgatives.

The time elapsed since ingestion is an important factor when considering evacuation of the stomach. To be most effective, therapy should be initiated early, and if time from ingestion can be accurately determined, certain guidelines are applicable. Most authors recommend emptying the stomach if the patient is seen within four hours of ingestion.[5] Salicylate overdose, one of the common drug poisonings in children, is an exception and stomach evacuation has proven valuable even after delays of nine to ten hours.[6] We have also obtained substantial amounts of particulate return after four hours in patients in whom there is severe central nervous system (CNS) depression or pronounced ileus. Therefore, in this set of patients, we advise evacuating the stomach even if six to eight hours have elapsed since ingestion. Matthew adds that emptying the stomach should also be undertaken ". . . if the time of ingestion is not known and the patient is unconscious."[6]

The two methods of emptying the stomach are induction of emesis or gastric aspiration-lavage. Despite much interest in the subject, neither method has been accepted as superior by all. Boxer and co-workers compared ipecac-induced vomiting with gastric lavage for acute salicylate intoxication in adolescents and found emesis more effective than lavage.[7] Corby and co-workers found apomorphine-induced vomiting preferable to lavage and ipecac-induced emesis less satisfactory than either in canine models.[8] Abdallah and Tye showed emetic-induced emesis superior to lavage.[9] However, Matthew feels the emetics may produce protracted vomiting, shock, CNS depression and greater tendency toward aspiration—and are therefore dangerous.[10] Although definite evidence showing one method superior to the other is lacking, most authorities prefer emesis for emptying the stomach when applicable.[2]

Physicians must be aware of the contraindications to the induction of emesis which include pronounced CNS depression, ingestion of caustic agents and ingestion of convulsants. In no patient should emesis be induced unless the patient is alert enough to communicate and a good gag reflex is present. With petroleum distillate poisoning many advise against the use of emesis,[2,11] but Shirkey recommends the use of syrup of ipecac in patients who have ingested large quantities of these hydrocarbons and are seen early.[12]

There is also controversy regarding which pharmacological emetic is best. The two most popular agents are syrup of ipecac and apomorphine. Syrup of ipecac (not fluid extract of ipecac, which is 14 times more concentrated and should not be used) is readily available, acts both centrally and as a gastric irritant and is reliable.[11] However, it is adsorbed by activated charcoal, takes approximately 14 minutes to be effective[13] and requires a cooperative patient. The recommended dose is 15 to 20 ml in children and 30 ml in adults. At least a quart of water should be given to adults to facilitate absorption of the ipecac and to prevent dry retching. Proportionately smaller amounts of water are used in children. If the first dose is not successful in 20 to 30 minutes, a second dose should be administered.

Apomorphine is the other generally available emetic. An injection of 0.07 to 0.1 mg per kg of body weight is administered subcutaneously or intramuscularly and therefore can be given to an uncooperative patient. It acts centrally and has an onset of action of approximately four minutes.[13] Other advantages are that apomorphine is not affected by administration of activated charcoal and promotes proximal small bowel reflux.[8,11] The major disadvantage is that it is dispensed as a tablet and in most hospitals must be prepared fresh for injection each time it is to be used. Should one dose fail to induce vomiting, sub-

sequent doses are of no value and ipecac or lavage must be substituted. A controversial point is the degree of CNS depression which occurs with its use. Corby and Decker feel it causes little CNS depression and they endorse apomophine.[14] However, MacLean feels the CNS depression is significant enough to recommend ipecac instead.[13] We too have observed significant CNS depression with apomorphine in adults and also prefer ipecac. Should significant CNS depression or protracted vomiting occur, either might be reversed with the usual dose of naloxone.

Gastric aspiration-lavage is the technique of choice in overdosed patients who are suffering from CNS depression and therefore are not suitable for induction of emesis. If the ingested material contains petroleum distillates, use of lavage is again controversial because of the potential danger of aspiration. However, if large amounts of petroleum products are ingested and the patient is not a candidate for emesis, careful lavage should be undertaken.[12,15] When the ingested material is a convulsant or is caustic in nature, lavage is contraindicated.

The proper lavage technique is essential to avoid complications and provide maximum efficiency. The patient is placed on his left side in the Trendelenburg position.[10] To prevent pulmonary aspiration, a cuffed endotracheal tube should be inserted whenever possible. Suction apparatus must always be available in the event vomiting occurs. The lavage tube should be as large as possible (at least a 31 F in adults), and we have found it useful to cut supplemental large holes randomly over the distal three or four inches of the tube to facilitate removal of particles. Preferably the tube is passed through the mouth and is carefully checked for position to be sure it is not in the trachea or a large bronchus. A bite block or oral airway may be helpful to prevent occlusion of the tube by mouth closure. Aspiration of gastric contents is done first. Lavage is then carried out with approximately 300 ml of saline per run in adults and proportionately smaller amounts in children. The total volume of fluid used must be large (2 to to 8 liters). Saline is preferred because of the potential danger of dilutional hyponatremia with water but the possibility of hypokalemia, although rare, still exists. In the group of patients too depressed for induction of emesis yet too responsive to allow intubation, we feel cautious lavage is still indicated. In our experience, lavage can be accomplished with a very low incidence of pulmonary aspiration if done with care and attention is paid to details.

The uncertainties involving the techniques of gastric emptying have prompted a reevaluation of activated charcoal as a gastrointestinal tract decontaminant.[16] In 1963 Holt and Holz renewed interest in the use of activated charcoal,[17] but it remained for Corby and co-workers to emphasize its value.[16] Activated charcoal is the odorless, tasteless residue of various organic products.[18] It is a fine black powder with a large surface area and therefore is quite adsorbent. Sufficient tap water is added to the powder to bring all the charcoal into suspension. This aqueous slurry is either given to the patient to drink or administered via a nasogastric tube. Decker and associates have shown charcoal alone to be as effective as apomorphine-induced emesis in salicylate ingestion, but more importantly, demonstrated that emesis combined with charcoal is more valuable than either emesis or charcoal used alone.[19] Activated charcoal has a wide spectrum of activity which includes propoxyphene, barbiturates and glutethimide.[16,20] However, it is inactivated by cyanide and is a poor adsorbent of ferrous sulfate,[16] ethanol, methanol, caustic alkalis and mineral acids.[18]

Since activated charcoal is most effective if given early, it should be readily available for use outside the hospital by laymen or paramedical personnel. The recommended dose is based on the amount of drug ingested. A ratio of at least five grams of charcoal to each one gram of poison is recommended but a ten to one ratio is preferable, and is necessary if food is present in the stomach. If the amount of poison ingested is unknown, a dose of 15 to 30 grams is suggested. The poison-charcoal complex remains stable throughout the gastrointestinal tract and will turn the stool black as it is excreted. Since charcoal is free of side effects, it can be given without fear. However, its indiscriminate use may lead to a false sense of security for a physician,[18] and therefore a list of substances adsorbed by activated charcoal should be consulted.[20]

Several regimens of administration of activated charcoal are available. It may be given orally at the time of subcutaneous or intramuscular administration of apomorphine. Alternately, it may be given *following* ipecac-induced vomiting. Although this regimen has not been fully evaluated, it has been alluded to in the literature[16] and seems quite logical. It avoids the possible disadvantages of apomorphine yet allows use of the activated char-

coal adjunct. In our emergency department we prefer emesis to empty the stomach if no contraindications exist. Ipecac is routinely used and when vomiting has ceased, a slurry of activated charcoal is given. However, in an uncooperative but otherwise suitable patient apomorphine may be employed as the emetic with the charcoal given concomitantly.

If lavage must be employed, 50 grams of charcoal can be added to 500 ml of saline to use as the lavage fluid. This obscures one end point (clear return) of lavage, but provided large volumes are used, is a very satisfactory technique. We prefer routine saline lavage followed by 30 grams of activated charcoal left in the stomach at the end of the procedure.

To hasten elimination of ingested products from the gastrointestinal tract, the use of cathartics has been suggested despite little evidence proving their efficacy. De Castro feels laxatives are not as effective as gastric lavage or emesis but may serve as another adjunctive measure.[2] They should not be employed if corrosives have been ingested or for patients in whom electrolyte disturbances are shown to exist.[21] We prefer magnesium citrate, but sodium phosphate or sodium sulfate may also be used.

General Care

The general care of a severely ill overdose patient does not differ greatly from the care of any critically ill or comatose patient. Although specific antidotes are available for a small number of poisons,[21,22] supportive care must receive the major emphasis. Careful fluid and electrolyte balance, preventative skin care, prophylaxis against deep venous thrombosis and attention to urinary and intravenous catheter sites decrease rates of morbidity and mortality in such patients. Respiratory care must be particularly aggressive as pulmonary complications are the leading cause of death in overdosed patients.[20]

Despite seemingly adequate conservative therapy, special therapeutic approaches may be necessary in a minority of cases. Forced diuresis, alkalinization of urine, peritoneal or hemodialysis may be useful for a particular poison but none of these techniques is routinely indicated. Before undertaking a specialized form of treatment it is necessary to consider the metabolism and route or routes of excretion of the toxin as well as the experiences other physicians have had with treating similar overdoses.[20]

Conclusion

We have attempted to provide a concise treatment outline for a physician who is faced with an overdosed patient. It is hoped that adherence to these guidelines will help lower the morbidity and mortality of overdose.

Summary

Successful management of patients who have taken excessive quantities of a drug or poison depends on prompt recognition and treatment. After support of vital functions and rapid evaluation, early efforts are directed at minimizing further absorption of the toxin. Induction of emesis by syrup of ipecac or apomophine is usually the preferred method to empty the stomach in suitable patients. If lavage is employed, meticulous attention to details will decrease morbidity. Activated charcoal is a useful adjunct to therapy and can be used with emetics or lavage techniques. Cathartics may be used but their usefulness has not been proven.

REFERENCES

1. Matthew H: Acute poisoning—Some myths and misconceptions. Br Med J 1:519-522, 1971
2. De Castro F J: Principles of emergency treatment of poisoning in children. Pediatrician 2:47-59, 1973
3. Wilkinson GR: Treatment of drug intoxication—A review of some scientific principles. Clin Toxicol 3:249-256, 1970
4. Evans LEJ, Swainson CP, Roscoe P, et al: Treatment of drug overdosage with naloxone, a specific narcotic antagonist. Lancet 1:452-455, 1973
5. Matthew H: Gastric aspiration and lavage. Clin Toxicol 3: 179-183, 1970
6. Matthew H: Mackintosh TF, Tompsett SL, et al: Gastric aspiration and lavage in acute poisoning. Br Med J 1:1333-1337, 1966
7. Boxer L, Anderson FP, Rowe DS: Comparison of ipecac-induced emesis with gastric lavage in the treatment of acute salicylate ingestion. J Pediatr 74:800-803, 1969
8. Corby DG, Lisciandro RC, Lehman RH, et al: The efficiency of methods used to evacuate the stomach after acute ingestions. Pediatrics 40:871-874, 1967
9. Abdallah AH, Tye A: A comparison of the efficacy of emetic drugs and stomach lavage. Am J Dis Child 113:571-575, 1967
10. Matthew H, Lawson AAH: Treatment of Common Acute Poisonings. Edinburgh, E & S Livingstone, 1970
11. Thoman ME: The use of emetics in poison ingestions. Clin Toxicol 3:185-188, 1970
12. Shirkey HC: Treatment of petroleum distillate ingestion. Mod Treat 4:697-709, 1967
13. MacLean WC: A comparison of ipecac syrup and apomorphine in the immediate treatment of ingestion of poisons. J Pediatr 82:121-124, 1973
14. Corby DG, Decker WJ, Moran MJ, et al: Clinical comparison of pharmacologic emetics in children. Pediatrics 42:361-364, 1968
15. Done AK: The fuel shortage—A dangerous spin-off. Emergency Medicine 6:289-296, 1974
16. Corby DG, Fiser RH, Decker WJ: Re-evaluation of the use of activated charcoal in the treatment of acute poisoning. Pediatr Clin North Am 17:545-556, 1970
17. Holt LE, Holz PH: The black bottle. J Pediatr 63:306-314, 1963
18. Picchioni AL: Activated charcoal—A neglected antidote. Pediatr Clin North Am 17:535-543, 1970
19. Decker WS, Shpall RA, Corby DG, et al: Inhibition of aspirin absorption by activated charcoal and apomorprine. Clin Pharmacol Ther 10:710-713, 1969
20. Knepshield JH, Schreiner GE, Lowenthal DT, et al: Dialysis of poisons and drugs—Annual review. Trans Amer Soc Artif Int Organs 19:590-633, 1973
21. Dreisbach RH: Handbook of Poisoning, 8th Ed. Los Altos, California, Lang Medical Publications, 1974
22. Arena JM: Current status: The management and treatment of poisoning—General principles of treatment and specific antidotes. Mod Treat 8:461-502, 1971

Medical Information

Refer to: Simon RP: Syncope and transient loss of consciousness —Differential diagnosis and treatment (Medical Information). West J Med 123:164-170, Aug 1975

Syncope and Transient Loss of Consciousness

Differential Diagnosis and Treatment

Roger P. Simon, MD, *San Francisco*

TRANSIENT LOSS of consciousness is a common complaint in any emergency room or physician's office. In most cases the cause of such events is rapidly established, simple faints and epilepsy making up the majority of diagnoses. The challenge then is not to overlook the relatively less common and often less benign causes.

The differential diagnosis is presented here.

Simple Faints

Vasovagal disorders are exceedingly common and occur in all age groups (mean age is 40 years old). Males and females are affected equally. Common causes include emotional stimulation, injury, pain, sight of blood, sudden exposure to cold, fatigue, instrumentation and blood loss (for example, 5 percent of blood donors giving 500 ml experience syncope; 50 percent of patients donating 1,000 ml experience syncope).[1]

Vasovagal episodes begin in a standing or sitting position, never in a horizontal position. The prodrome lasts from between 10 and 20 seconds to a few minutes and can include weakness, lightheadedness, nausea, pallor, diaphoresis, salivation, blurred vision and tachycardia. Subsequently, the patient falls to the ground, pale and diaphoretic, with mydriatic pupils and slow, weak pulse (tachycardia becomes bradycardia as consciousness is lost). Movements may be noted during unconsciousness. They are mainly tonic, often opisthotonic.[2] Occasionally urinary incontinence or seizure-like tonic-clonic movements are noted.[3] Tongue biting is rare. The electroencephalographic electrical activity becomes flat, clearly differentiating vasovagal episodes from seizures. Secondary cerebral hypoxia and tonic-clonic movements are more likely to occur if the patient is kept in an upright position.

The patient is alert and awake shortly after assuming a horizontal position (seconds to a few minutes). Residual nervousness, dizziness, headache, nausea and vomiting, pallor and diaphoresis are not uncommon. A desire to defecate may be noted. If the patient stands during the next thirty minutes, syncope may recur.

Physiologically, both decreased arterial tone and bradycardia combine to produce central nervous system hypoperfusion[4] although examples of pure vasodepressor (hypotension) or cardioinhibitory (bradycardia) syncope have been described.[2] Syncope without alteration in blood pressure or heart rate is termed cerebral[5] but its existence is doubtful.[2] Ocular compression[2] (oculovagal reflex) or the Valsalva maneuver[6] may be helpful in showing abnormal sensitivity to vagal stimulation and thus providing evidence of a vasovagal cause for episodes of loss of consciousness in a given patient. In one series, ocular compression produced loss of consciousness in 20 percent of patients fainting, and transient cardiac standstill in 70 percent.[2]

In view of the pathophysiology of these episodes, trials of belladonna alkaloids, ergot alkaloids or barbiturates (or combinations of these) have been recommended as therapy.[7,8]

Seizures

Seizures are an exceedingly common cause of episodic loss of consciousness, affecting 0.4 percent of the population. The history of a seizure is one of sudden onset of symptoms. An aura, if present, is brief but may have localizing significance such as olfactory, gustatory or deja-vu auras in temporal lobe seizures; focal, sensory or motor symptoms in frontoparietal lobe foci; visual scotomata in the occipital lobe. Seizures may begin in any position and 20 percent of persons with epilepsy have seizures only during sleep. Generalized tonic-clonic movements are commonly noted; however, a predominance of somatosensory symp-

From the Department of Neurology, University of California, San Francisco.

Reprint requests to: R. P. Simon, MD, Department of Neurology, University of California, San Francisco, San Francisco, CA 94143.

toms, tonic posturing or temporal lobe manifestations (auditory, vertiginous, visceral phenomena; psychomotor automatisms) make diagnosis more difficult. Cyanosis is frequent during seizures; pallor is uncommon; breathing is often stertorous.

In the differential diagnosis of episodic loss of consciousness the most distinctive feature of epilepsy is a period of altered consciousness (postictal state) following the seizure. This period is usually limited to a few minutes of disorientation. However, prolonged alteration of consciousness may occur during status epilepticus, and is seen postictally in patients with diffuse structural cerebral damage (for example, status post multiple cerebral infarctions, senile dementia) or following seizures resulting from acute encephalitis or hyponatremia.[9]

Findings on physical examination during the postictal state commonly will be normal or will show only positive Babinski signs. The patient frequently experiences headache. Pupils are always reactive to light, even in unresponsive patients. Lateralizing motor findings or focal motor onset may localize the central nervous system lesion. The epileptic postictal state stands in strong contrast to vasovagal episodes where consciousness and orientation are regained in close aposition. A history of urinary incontinence or of a few jerking or clonic movements is of dubious differential value since these symptoms can be found in both simple vasovagal syncope and in epilepsy.

Although idiopathic epilepsy is by far the most common cause of seizures, important additional causes include purulent meningitis, uremia, acute anoxia from any cause (such as cardiac arrest or arrhythmia), hyponatremia, hypoglycemia, hypocalcemia, hypertensive encephalopathy, rapid decrease in anticonvulsant drug levels, embolic cerebrovascular disease and head trauma. Acute withdrawal from ethanol in chronic abusers may produce seizures, 90 percent of which occur during the first 7 to 48 hours.[10] Seizures are generalized and occur in a brief flurry, most commonly one to six in number. Medical intervention is usually unnecessary since the seizures are selflimiting. Diphenylhydantoin sodium (Dilantin®) therapy is said to be ineffective acutely but this may be due to the time needed to administer a therapeutic dose.[11] There is some suggestion that barbiturates[12] or chlordiazepoxide[13] might be effective prophylactically, but patient compliance is of course a problem. Phenobarbital (200 mg given intramuscularly one time) is adequate acutely if needed. Drug withdrawal seizures are seen following withdrawal from daily doses of sodium secobarbital (Seconal®) greater than 450 mg a day or the equivalent amount of other sedative hypnotics (although seizures are more commonly seen when doses of 600 to 800 mg have been used).[14] Sedative-hypnotic drug abuse should be treated in hospital by gradual withdrawal (approximately one therapeutic dose daily).

Once a seizure disorder is suspected, supportive evidence can be gained from electroencephalography, but findings on a single tracing can be normal in more than 40 percent of patients with epilepsy.[15] Anticonvulsant therapy is dictated by the cause of the seizure and varies from brief observation (ethanol withdrawal) to chronic anticonvulsant therapy (idiopathic epilepsy). If an anticonvulsant is indicated, administration of Dilantin (1,000 mg given orally during the first 24 hours, 500 mg given orally during the second 24 hours and 300 mg given orally each day thereafter) is a common first-line approach while diagnostic studies are being made. This regimen will provide therapeutic blood levels in 24 hours; 1 gram given intravenously (50 mg per minute) will produce a rapid therapeutic response. Nystagmus on lateral gaze is correlated with Dilantin levels above 2 mg per 100 ml and is therefore a helpful indicator of adequate anticonvulsant therapy (minimum therapeutic levels are 1 to 2 mg per 100 ml).[16]

Cardiovascular Syncope

Syncope in the recumbent posture is very suggestive of a cardiac-related cause. It may occur secondary to sinus arrest, bradyarrhythmia (with rate below 30) or tachyarrhythmia. Acute myocardial infarction is an important exclusion; in one series, loss of consciousness was reported in ten of 200 such patients.[17]

Stokes-Adams

Syncope due to transient bradyarrhythmias and asystole has been termed the Stokes-Adams syndrome.[18] Episodes are as common in men as in women and occur mainly in the sixth or seventh decade. There is often no prodrome. Onset is rapid with loss of consciousness in 3 to 5 seconds —or within 15 seconds if the patient is recumbent. Convulsion and fecal incontinence are not uncommonly seen as duration of cerebral hypoperfusion becomes greater. Recovery of consciousness

is rapid, within seconds to a few minutes. A postictal confusional state is expected in patients who convulse; otherwise, no residual is seen.

Findings on electrocardiograms made following Stokes-Adams attacks can be normal, especially after sinus arrest or third degree atrioventricular block.[19] Several syndromes of episodic loss of consciousness with prolonged Q-T interval have been described;[20] such as congenital deafness, syncope, prolonged Q-T interval and sudden death secondary to ventricular fibrillation.[21] Tape recorded continuous portable electrocardiograph monitoring and measurement of cardiac enzymes are essential aspects of the evaluation.

Tachyarrhythmias

Tachyarrhythmias with heart rates greater than 180 to 200 beats per minute produce syncope in approximately 50 percent of patients, depending on age.[22] Periods of asystole sufficient to produce syncope have been observed following the cessation of a supraventricular tachycardia[23] (the sick sinus syndrome). While digitalis may be the drug of first choice for prophylaxis in some supraventricular arrhythmias, a pacemaker may be required for the sick sinus syndrome.[24]

Aortic Stenosis

Loss of consciousness secondary to aortic stenosis has been observed in all age groups. Episodes are especially common following exercise and are often associated with dyspnea, angina and diaphoresis. Two phases are recognized: acute left ventricular failure with normal sinus rhythm lasting 40 seconds, and a second stage of ventricular arrhythmia or cardiac standstill producing apnea, cyanosis and convulsion. Sudden death may result.[25]

On examination, there is a carotid pulse with slow upstroke and low peak (pulsus parvu et tardus) in most patients with hemodynamically-significant aortic stenosis, but this sign may be absent. A systolic thrill is perhaps better correlated with aortic valve pathology (in combination with the characteristic murmur). Failure to find evidence on x-ray studies of aortic valve calcification in patients over 35 makes diagnosis of aortic stenosis highly suspect.[26] Symptomatic aortic stenosis (angina, failure, syncope) requires valve replacement since average survival following syncope is three years.[27]

IHSS (Idiopathic Hypertrophic Subaortic Stenosis)

Most commonly IHSS[28] becomes symptomatic between the second and fourth decades. Syncope, frequently associated with exercise, was noted in 30 percent of cases in one series and was the presenting symptom in 10 percent of cases (with orthostatic and post-tussive syncope also reported); dyspnea, however, was the most common presenting symptom (60 percent of all cases).

On examination, suggestive features are a double apical impulse, precordial thrill, paradoxically split second sound, third and fourth heart sounds, and a long systolic murmur with mid-systolic accentuation maximum at the lower left sternal border or apex. Syncope in IHSS may not be associated with hemodynamic evidence of left ventricular outflow obstruction. Propranolol has been the most useful therapeutic agent.

Pulmonary Hypertension

Syncope, often secondary to effort, can be associated with pulmonary hypertension and may be the presenting symptom. Signs of right ventricular failure may be found: parasystolic heave, increased pulmonic second sound (P_2), murmur of pulmonic insufficiency or electrocardiographic evidence of right ventricular hypertrophy. Pulmonary emboli are often an unrecognized cause of pulmonary hypertension and may present with only sudden loss of consciousness.[29]

Other cardiac lesions associated with loss of consciousness are tetralogy of Fallot, ball variance in valve prostheses and atrial mysoma.

Cerebral Vascular Syncope

Cerebral vascular disease is an often diagnosed but actually uncommon cause of episodic unconsciousness. Several distinct entities deserve comment.

Basilar Artery Insufficiency

Basilar artery insufficiency and basilar artery transient ischemic attacks (TIA's) occur most commonly after the sixth decade. Episodes begin almost exclusively in the sitting or standing position.[30] The symptom complex of diplopia, vertigo, dysphasia, dysarthria, various sensory or motor symptoms, drop attacks and occipital headaches suggest diffuse areas of brain stem ischemia. Episodes are of sudden onset and brief duration (seconds to minutes). Isolated episodes of unconsciousness occur only rarely. When loss of con-

sciousness is included in the symptom complex, recovery is prolonged (30 to 60 or more minutes). Transient vertebral artery occlusion secondary to nuchal compression on head turning or to cervicocranial anomalies is one treatable cause of basilar artery ischemia.[31] In general, however, the therapy for these disorders is unclear; and recurrent episodes have been observed in 68 percent of cases and strokes in 18 percent of cases in one study.[32] Anticoagulation with sodium warfarin (Coumadin®)[33] or acetylsalicylic acid (aspirin) should be employed for at least two months.[34]

Migraine

Syncope, often secondary to rapid standing, has been reported in 10 percent of 500 patients with migraine,[35] suggesting that the loss of consciousness is due to orthostatic hypotension. In the specific syndrome of basilar artery migraine,[36] the migrainous vasoconstriction involves the basilar artery and produces symptomatology similar to basilar artery transient ischemic attacks. Most cases described occur in adolescent girls; however, additional documented cases in adults support this clinical entity.[37] Medical therapy with antimigraine drugs is often effective.

Takayasu's Disease

Takayasu's disease (aortic arch syndrome, pulseless disease) is a panarteritis of the great vessels occurring nearly exclusively in girls. Prominent symptoms include those of hypoperfusion of the central nervous system—such as decreased vision and confusion. Syncope or loss of consciousness was noted in 75 percent of patients with this disease in one series, particularly following exercise, standing or head movement.[38] On physical examination, decreased or absent peripheral pulses and low recorded blood pressure in the arms are found.

Carotid Sinus Syncope

Carotid sinus syncope is a rare condition, though commonly discussed. Men are affected twice as often as women and most have passed the sixth decade of life. Classically, pressure of the carotid sinus by a tight collar, neck mass, cervical nodes or tumor causes vagal stimulation of the sinoatrial and atrioventricular nodes and a sympathetic inhibition. Bradycardia and hypotension result producing syncope; the bradycardia is blocked by administration of atropine.[39] Many cases misdiagnosed as hypersensitive carotid sinus have been found to be secondary to ipsilateral carotid compression with contralateral carotid occlusion. Diagnosis, then, demands knowledge of the patency of the cerebral circulation, or at least the presence of good carotid pulses bilaterally with loss of consciousness on carotid stimulation without manual occlusion of the vessel.[40]

Miscellaneous

Orthostatic Hypotension

Orthostatic hypotension occurs in males slightly more frequently than in females. It is most common in the sixth and seventh decades but may also appear in the teens. Drug ingestion is a major cause; a list of drugs commonly involved is given in Table 1.[41]

Loss of consciousness usually occurs as a result of rapid standing. Prolonged motionless standing (especially following exercise) and standing after prolonged bed rest (especially in elderly patients) are other frequent causes. Orthostatic syncope may be the presenting symptom of acute blood loss or Addison's disease, or may follow sympathectomy. Orthostatic changes can be associated with peripheral neuropathies—such as diabetes mellitus (orthostatic changes occur in 30 percent of patients), alcoholism, Guillain-Barre syndrome or amyloidosis. With central nervous system lesions, autonomic nervous system involvement produces orthostatic hypotension in Wernicke's encephalopathy, the myelopathy of multiple sclerosis, and tabes dorsalis. Idiopathic orthostatic hypotension when part of the Shy-Drager syndrome is characterized by anhidrosis, sphincter disturbances, parkinsonism and impotence; no postural change in pulse is seen.[42]

TABLE 1.—*Drugs Commonly Involved in Orthostatic Hypotension*

Amitriptyline	Iopanoic acid
Benzothiadiazines (Chlorothiazide, hydrochlorothiazide polythiazide)	Levodopa
Bretylium	Lidocaine
Chlorisondamine	Monoamine oxidase inhibitors
Clonidine	Methotrimeprazine
Desipramine	Methyldopa
Furosemide	Methysergide
Guanacline	Nitroglycerine
Guanethidine	Pentolinium
Guanoxan	Phenoxybenzamine
Hexamethonium	Procarbazine
Imipramine	Protriptyline
	Reserpine
	Thiothixene

Important studies include orthostatic blood pressure measurements, hematocrit, stool guaiac and—in equivocal cases—tilt-table testing.[43] Immediate therapy includes discontinuing any offending medication, gradual standing, placing head of bed on blocks and use of support stockings. Longer-term therapy is dictated by the specific cause of the hypotension. Administration of 9-alpha-fluorohydrocortisone has been effective in idiopathic cases, beginning with 0.1 mg daily with gradual increases as necessary to as much as 1.0 mg daily.[44,45]

Hyperventilation

Hyperventilation is a common cause of altered consciousness manifested by light-headedness, shortness of breath, numbness and tingling (especially circumoral) and muscular twitching. Its culmination in syncope is unusual; however, the occurrence has been described.[46] Loss of consciousness is produced by hypocapnea-induced cerebral vasoconstriction resulting in hypoxia. Women are affected much more often than men and patients are usually in the third or fourth decade. This disorder is most often benign with anxiety as a prominent precursor but cardiopulmonary causes for dyspnea must be excluded. The syndrome commonly occurs when a patient is lying down, a helpful differential diagnostic point. Tetany is rare although nearly diagnostic. Patients often claim prolonged unconsciousness; upon close questioning, however, this is rarely the case. Often, hyperventilation at the examiner's request will duplicate symptoms.

Post-tussive Syncope

Post-tussive syncope occurs primarily in elderly men with chronic obstructive pulmonary disease but has been reported in children.[47] Coughing, not necessarily prolonged, immediately precedes the attack which is notable for its possible occurrence when the patient is lying down. Prodromal symptoms of syncope are often absent, and the duration of unconsciousness is less than one minute. Recovery is immediate. A history of similar episodes is common, and symptoms may be duplicated by having the patient cough on request. The cause may be a decrease in cerebral blood volume due to the pronounced increase in intracranial pressure during a cough paroxysm.[47] A role of cerebral vascular disease affecting the carotid sinus has also been suggested.[48]

Micturition

Micturition syncope is observed almost exclusively in men, probably because of the standing position for urination. Symptoms may occur immediately before, during or after micturition. Episodes nearly always occur at night and may be secondary to orthostatic hypotension following the prolonged recumbency of sleep, plus vagal induced bradycardia.[49]

Glossopharyngeal Neuralgia

This is a syndrome of intermittent agonizing paroxysmal pain, localized to the tonsilar pillar or, occasionally, the external auditory meatus. It has been associated with syncope felt to be secondary to activation of glossopharyngeal-vagal reflex arc.[50] Atropine and Dilantin have been used to treat syncope in this condition but carbamazepine (Tegretol®), 400 to 1,000 mg every day, is clearly the drug of choice for the entire syndrome.[51]

Hysteria

Hysteria is a diagnosis of exclusion and is overdiagnosed. Suggestive features are lack of prodrome, possible secondary gain, bizarre postures and movements, lack of pallor and prolonged unconsciousness. Generally, the patient is young or has a well-documented history of hysterical reaction to stress. Without such history, the diagnosis of hysteria after the midtwenties is suspect.

During episodes of hysterical unconsciousness, ice-water irrigation against the tympanic membrane (30 ml of water with the patient's head at 30°) will produce brisk nystagmus with the fast component to the opposite side. If the patient is unconscious because of an organic cause the eyes will remain tonically deviated to the side of the irrigation.[52]

Narcolepsy

Males are affected by narcolepsy as often as females; the onset of the syndrome is most commonly between the second and third decades. Sleep attacks are often part of a syndrome characterized by a quartet as follows: (1) narcolepsy (sleep attacks)—one to multiple episodes or irresistible somnolence daily lasting minutes to several hours and producing a refreshing sleep; (2) cataplexy—sudden loss of postural muscle tone, usually preceded by an emotional stimulus (startle, laughing, fear, cough); (3) sleep paralysis —immobility of extremity muscles lasting seconds

during awakening or falling asleep; (4) hypnagogic hallucinations—vivid dreams, or nightmares, often occurring as the patient is falling asleep. One or any combination of the quartet may be found.[53] Antinarcoleptic treatment classically includes methylphenidate (Ritalin®) 40 to 80 mg every day, dextroamphetamine or ephedrine. Imipramine, 25 mg three times a day, is effective against cataplexy, sleep paralysis and hypnagogic hallucinations.[54]

Meniere's Disease

Meniere's disease is characterized by recurrent paroxysmal attacks of severe vertigo lasting up to several hours. Tinnitus and progressive hearing loss are found. Loss of consciousness of a few seconds is found in a small percentage of patients.[55] Basilar artery ischemic attacks pose a common differential diagnostic problem; scintillating scotomata accompanying the vertiginous attacks stamp the diagnosis as basilar artery ischemia. Dimenhydrinate (Dramamine®), 50 mg three times a day, is often helpful.

Swallow Syncope

This is a rare but potentially fatal form of syncope following swallowing. In most cases structural disease of the esophagus is felt responsible but cardiac and central nervous system lesions have been found. The attacks are aborted by atropine and the syndrome is felt to be vagally mediated.[56]

Summary

The differential diagnosis of episodic loss of consciousness has been presented. One should approach the problem by first considering simple faints or epilepsy. The various less common causes of a cardiovascular or cerebrovascular nature, as well as others, have been discussed here. It is important that these less commonly seen causes, which are often more serious, not be overlooked when diagnosing and treating transient loss of consciousness.

REFERENCES

1. Barcroft H, Edholm OG, McMichael J, et al: Post hemorrhagic fainting. Lancet 1:489-491, 1944
2. Gastaut H: Electro-encephalographic study of syncope. Lancet 2:1018-1025, 1957
3. Duvoisin RC: Convulsive syncope induced by the Weber maneuver. Arch Neurol 7:219-226, 1962
4. Epstein SE, Stampfer M, Beiser GD: Role of the capacitance and resistance vessels in vasovagal syndrome. Circulation 37:524-533, 1968
5. Engel GL: Fainting. Springfield, Ill., Charles C Thomas, 1950, p 53
6. Duvoisin RC: The Valsalva maneuver in the study of syncope. Electroen Neurophysiol 13:622-626, 1961
7. Gastaut H: Syncope, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology, Vol 15. New York, American Elsevier Publishing Company, 1974, p 815
8. Glick G, Yu PN: Hemodynamic changes during spontaneous vasovagal reactions. Am J Med 34:42-51, 1963
9. Plum F, Posner JB (Eds): Diagnosis of Stupor and Coma. Philadelphia, F. A. Davis Company, 1972, p 214
10. Victor M, Brausch C: The role of abstinence in the genesis of alcoholic epilepsy. Epilepsia 8:1-20, 1967
11. Victor M: The treatment of alcoholism, chap 14, *In* International Encyclopedia of Pharmacology and Therapeutics, Sec 20, Vol II. Elmsford, NY, Pergamon Press, Inc., 1970
12. Essig CF, Jones BE, Lam RC: The effects of pentobarbital on alcohol withdrawal in dogs. Arch Neurol 20:554-558, 1969
13. Kaim SC, Klett CJ, Rothfeld B: Treatment of the acute withdrawal state: A comparison of four dogs. Am J Psychiat 125: 1640-1646, 1969
14. Fraser HF: Degree of physical dependence induced by secobarbital or phenobarbital. JAMA 166:126-129, 1958
15. Marsan CA, Zivin LS: Factors related to the occurrence of typical paroxysmal abnormalities in the EEG records of epileptic patients. Epilepsia 11:361-381, 1970
16. Kutt H, McDowell F: Management of epilepsy with diphenylhydantoin sodium. JAMA 203:969-972, 1968
17. Cookson H: Fainting and fits in cardiac infarction. Br Heart J 4:163-173, 1942
18. Pomeranz B, O'Rourke RA: The Stokes-Adams syndrome. Am J Med 46:941-960, 1969
19. Friedberg CK: Syncope: Pathological physiology—Differential diagnosis and treatment. Mod Conc Cardiovasc Dis 40:55-63, 1971
20. Singer PA, Crampton RS, Bass NH: Familial Q-T prolongation syndrome. Arch Neurol 31:64-66, 1974
21. Olley PM, Fowler RS: The surdo-cardiac syndrome and therapeutic observations. Br Heart J 32:467-471, 1970
22. Wolfe L: The cardinal manifestations of paroxysmal tachycardia. N Engl J Med 232:527-530, 1945
23. Bradlow BA: Supraventricular paroxysmal tachycardia interrupted by reported episodes of cardiac standstill with syncopal attacks. Chest 58:122-128, 1970
24. Easley RM, Goldstein S: Sino-atrial syncopy. Am J Med 50:166-177, 1971
25. Schwartz LS, Goldfischer J, Sprague GJ, et al: Syncope and sudden death in aortic stenosis. Am J Card 23:647-658, 1969
26. Lee JE, Killip T, Plum F: *In* Barowdess JA (Ed): Diagnostic Approaches to Presenting Syndromes. Baltimore, Williams and Wilkins, 1971, p 149
27. Ross J, Braunwald E: Aortic stenosis. Circulation 37-38 (Suppl 5):61-67, 1968
28. Braunwald E, Lambrew CT, Rockoff SD, et al: Idiopathic hypertrophic subaortic stenosis. Circulation 29-30 (Suppl 4):1-115, 1964
29. Dressler W: Effort syncope as an early manifestation of primary pulmonary hypertension. Am J Med Sci 223:131-143, 1952
30. Plum F, Posner JB (Eds): Diagnosis of Stupor and Coma. Philadelphia, F. A. Davis Co., 1972, p 127
31. Denny-Brown D: Recurrent cerebrovascular episodes. Arch Neurol 2:194-210, 1960
32. Baker RN: Prospective study of transient ischemic attacks. *In* Toole JF, Moossy J, Janeway R (Eds): Cerebral Vascular Disease. New York, Grune & Stratton, 1971
33. Millikan CH, Siekert RG, Shick RM: Studies in cerebrovascular disease—III. The use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. Mayo Clin Proc 30:116-126, 1955
34. Whisnant JR, Matsumoto N, Flueback LR: The effect of anticoagulant therapy on the prognosis of patients with transient cerebral ischemia attacks in a community. Mayo Clin Proc 48: 844-848, 1973
35. Selby G, Lance JW: Observations on 500 cases of migraine and allied vascular headaches. J Neurol Neurosurg Psychiat 23: 23-32, 1960
36. Bickerstaff ER: Impairment of consciousness in migraine. Lancet 2:1057-1059, 1961
37. Lees F, Watkins SM: Loss of consciousness in migraine. Lancet 2:647-650, 1963
38. Currier RD, DeJong RN, Bole GG: Pulseless disease: Central nervous system manifestations. Neurology 4:818-830, 1954
39. Thomas JE: Hyperactive carotid sinus reflex and carotid sinus syncope. Mayo Clin Proc 44:127-139, 1969
40. Ebert RV: Syncope. Circulation 27:1148-1155, 1963
41. Meyler L, Herxheimer A (Eds): Side effects of drugs. Excerpt Med, Amsterdam 1972
42. Shy GM, Drager GA: A neurological syndrome associated with orthostatic hypotension. Arch Neurol 2:511-527, 1960
43. Norris AH, Shock NW, Yiengst MJ: Age changes in heart rate and blood pressure responses to tilting and standardized exercise. Circulation 8:521-526, 1953

44. Bannister R, Ardill L, Fentem P: An assessment of various methods of treatment of idiopathic orthostatic hypotension. Q J Med 38:377-395, 1969

45. Frick MH: 9-alpha-fluorohydrocortisone in the treatment of postural hypotension. Acta Med Scand 179:293-299, 1966

46. Wright EK, McIntosh HD: Syncope: A review of pathophysicological mechanisms. Prog Card Dis 13:580-594, 1971

47. McIntosh HD, Estes EH, Warren JV: The mechanism of cough syncope. Am Heart J 52:70-82, 1956

48. Sutherland JM, Bournon DA, Tyler JH: Cough syncope with suggestions as to the possible role played by cerebral atherosclerosis. Med J Aust 1:39-42, 1965

49. Donker DNJ, Robles de Medina EO, Kieft J: Micturition syncope. Electroen Neurophysiol 33:328-331, 1972

50. Kong Y, Heyman A, Entman ML, et al: Glossopharyngeal neuralgia associated with bradycardia, syncope, and seizures. Circulation 30:109-113, 1964

51. Crill WE: Carbamazine. Ann Intern Med 79:844-847, 1973

52. Plum F, Posner JB (Eds): Diagnosis of Stupor and Coma. Philadelphia, F. A. Davis Company, 1972, p 218

53. Sours JA: Narcolepsy and other disturbances in the sleep-waking rhythm—A study of 115 cases with review of the literature. J Nerv Ment Dis 137:525-542, 1963

54. Guilleminault C, Carskadon M, Dement WC: On the treatment of rapid eye movement narcolepsy. Arch Neurol 30:90-93, 1974

55. Edwards CH: Neurology of Ear, Nose, and Throat Disease. London, Butterworth and Co., Ltd., 1973, p 142

56. Levin B, Posner JB: Swallow syncope. Neurology 22:1086-1093, 1972

86th Annual Meeting

Washington State Medical Association

OLYMPIC HOTEL • SEATTLE, WASHINGTON • SEPTEMBER 19-22, 1975

THE 1975 ANNUAL MEETING of the Washington State Medical Association will be held September 19-22, at the Olympic Hotel, Seattle. A preliminary copy of the scientific program will be mailed to all WSMA members and it is available to nonmembers by writing to:

WSMA Convention Manager
444 N.E. Ravenna Boulevard
Seattle, Washington 98115

SCIENTIFIC SESSIONS INCLUDE:

- **Thoracic and Allergy**
- **Aging as Viewed by the Specialists**
- **Psychopharmacology**
- **National Health Insurance**
- **Ophthalmology**
- **Therapy of Major Burns**
- **Gastroenterology**
- **Emergency Medicine**
- **Regionalization of Perinatal Care**
- **Pediatric-ENT**
- **Pain of the Upper Extremity**
- **Anesthesiology**
- **Professional Liability Problem**
- **Orthopedic, Surgical, and General Papers from Members and Guests**

GUEST SPEAKERS

PAUL B. BEESON, MD, Seattle
Distinguished Physician of the Veterans Administration and Professor of Medicine, University of Washington
- **The English System of National Health Care**

DAVID R. BOYD, MDCM, Hyattsville, Maryland
Director, Division of Emergency Medical Services Department of Health, Education, and Welfare
- **Current Overview of Emergency Services Delivery in the USA**
- **The Emergency Specialist and His Role in the Future Practice of Medicine**

JORDAN N. FINK, MD, Milwaukee, Wisconsin
Professor of Medicine, Chief, Allergy Section, The Medical College of Wisconsin, Wood Veterans Administration Hospital
- **Environmental Asthma, Allergy Testing and the Role of Immunotherapy**
- **Extrinsic Allergic Alveolitis**

GERALD A. GRONERT, MD, Rochester, Minnesota
Assistant Professor, Mayo Medical School
- **Methods and Mechanisms for Hypotensive Anesthesia**
- **Hypotensive Anesthesia for Neurosurgery**

HOWARD HASSARD, LLB, San Francisco
Legal Counsel, California Medical Association
- **No-Fault or Medical Injury Compensation**

THOMAS C. HOSHAW, MD, Missoula, Montana
- **Otitis/Sinusitis—Surgical Aspect**

LELAND B. HOUSMAN, MD, San Diego
- **The Emergency Treatment of Severe Chest Trauma**

JON I. ISENBERG, MD, Los Angeles
Chief, Gastroenterology Division, Wadsworth Veterans Administration Hospital; Associate Professor of Medicine, University of California, Los Angeles; Director, Gastroenterology Training—UCLA-Wadsworth Gastroenterology Training Program
- **The Future in Medical Therapy for Peptic Ulcer Disease**
- **Use of Antacids and Anticholinergics in Treatment of Peptic Ulcer**

WALTER KIRKENDALL, MD, Houston
Professor of Medicine and Head of the Department of Medicine, University of Texas Medical School at Houston
- **The Emergency Management of Hypertension, Congestive Heart Failure, and a Review of the Clinical Pharmacology of Diuretics**

DAVID H. KNOTT, MD, Memphis
Alcohol and Drug Research Center, Tennessee Psychiatric Hospital and Institution
- **Treatment of the Acute and Chronic Alcoholic Patient in the Emergency Department**

RICHARD G. LAYTON, Chicago
Assistant Director, Division of Public Affairs, American Medical Association
- **Federal Government and Congressional Proposals to Solve the Malpractice Problem**

WALTER McCLURE, PhD, Minneapolis
Senior Policy Analyst and Associate Director, Health Policy Group, InterStudy
- **Objectives for National Health Insurance**

IRWIN R. MERKATZ, MD, Cleveland
Robert Wood Johnson Foundation
- **Regionalization of Perinatal Care**

CRAWFORD MORRIS, LLB, Cleveland
- **How to Avoid Malpractice Suits Against Yourself and Your Associates**
- **The Present Court System**

JAY A. NADEL, MD, San Francisco
Professor of Medicine and Radiology and Staff Member of the Cardiovascular Research Institute, University of California, San Francisco
- **Pathophysiologic Mechanism of Asthma—Cholinergic**
- **Pharmacologic Mechanism in Treatment of Asthma**

LLOYD H. NYHUS, MD, Chicago
- **Surgical Therapy of Peptic Ulcer Disease**

KENNETH T. RICHARDSON, MD, FACS, Anchorage, Alaska
Consultant in Ophthalmology to the Surgeon General of the U.S. Air Force
- **Medical Management of the Glaucomas**
- **Surgical Management of the Glaucomas**

LESTER F. SENGER, Hartford, Connecticut
Vice President, Industry Affairs, Casualty & Surety Division, Aetna Life & Casualty
- **Insurance Industry Proposals**

101st Annual Session
Oregon Medical Association

SEPTEMBER 10-12, 1975

HILTON HOTEL • PORTLAND, OREGON

The Oregon Medical Association's membership takes great pride in extending an invitation to fellow physicians to attend its annual scientific session during OMA's 101st year

General Sessions

Wednesday afternoon through
Friday afternoon

SOMMER MEMORIAL LECTURES

JAMES V. WARREN, MD
Professor and Chairman, Department of Medicine
Ohio State University College of Medicine, Columbus

ARTHUR C. BEALL, MD
Department of Surgery, Baylor College of Medicine
Texas Medical Center, Houston

ERIC W. FONKALSRUD, MD
Professor and Chief of Pediatrics
University of California School of Medicine, Los Angeles

GUEST SPEAKER

JOHN R. WARD, MD
Chief, Division of Arthritis
University of Utah College of Medicine, Salt Lake City

Half-Day Seminars

Wednesday Afternoon, September 10
- Professional Liability

Friday Afternoon, September 12
- Quality of Life

Limited Registration Short Courses

- Endocrine Disorders
- Practical Office Genetics
- Perinatal Problems
- Rapid Evaluation and Treatment of the Severely Traumatized Patient
- Fluid and Electrolyte Problems
- Antibiotics—New and Current
- Office Gynecology
- Casting and Treatment of Common Fractures
- Urinary Tract Infection
- What To Do for the Sore Neck and Back

Specialty Section Programs

- General Practice
- Internal Medicine
- Radiology
- Neurology
- Neurosurgery

For program, reservations and information contact: OREGON MEDICAL ASSOCIATION
2164 SW PARK PLACE
PORTLAND, OREGON 97205
Telephone (503) 226-1555

in memoriam

Balius, Edward Francis, Stockton. Died May 26, 1975 in Stockton, aged 40. Graduate of Loyola University of Chicago, Stritch School of Medicine, Chicago, 1960. Licensed in California in 1961. Dr. Balius was a member of the San Joaquin County Medical Society.

Bell John C., Los Angeles. Died April 28, 1975 in Los Angeles of a ruptured abdominal aortic aneurysm, aged 73. Graduate of College of Osteopathic Medicine and Surgery, Des Moines, 1926. Licensed in 1926. M.D. degree from California College of Medicine, 1962. Dr. Bell was a member of the Los Angeles County Medical Association.

Blong, Peter H., Alhambra. Died June 7, 1975 in Alhambra of carcinoma of the prostate, aged 89. Graduate of Temple University School of Medicine, Philadelphia, 1910. Licensed in California in 1921. Dr. Blong was a member of the Los Angeles County Medical Association.

Crabtree, Hodge N., San Diego. Was killed May 26, 1975 in an automobile accident about 120 miles south of Mexicali, aged 50. Graduate of the University of Michigan Medical School, Ann Arbor, 1948. Licensed in California in 1953. Dr. Crabtree was a member of the San Diego County Medical Society.

Dwyer, William Francis, San Francisco. Died May 30, 1975, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1935. Licensed in California in 1936. Dr. Dwyer was a member of the San Francisco Medical Society.

Fitzgibbon, Joseph Paul, Palos Verdes. Died March 12, 1975 in Long Beach of carcinoma of the colon, aged 72. Graduate of Rush Medical College, Chicago, 1932. Licensed in California in 1932. Dr. Fitzgibbon was a member of the Los Angeles County Medical Association.

Flynn, George W., Petaluma. Died June 2, 1975 in Petaluma of heart disease, aged 60. Graduate of St. Louis University School of Medicine, St. Louis, 1943. Licensed in California in 1953. Dr. Flynn was a member of the Sonoma County Medical Association.

Griffiths, Robert Owen, Redding. Died June 19, 1975 in Long Beach, aged 43. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1956. Licensed in California in 1957. Dr. Griffiths was a member of the Los Angeles County Medical Association.

Haschka, August J., jr., Malibu. Died May 6, 1975, aged 58. Graduate of Marquette University School of Medicine, Milwaukee, 1951. Licensed in California in 1952. Dr. Haschka was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Hawes, Ralph E., Huntington Beach. Died January 9, 1975 in Newport Beach of carcinoma of the pancreas, aged 79. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1922. Dr. Hawes was a retired member of the Los Angeles County Medical Association and the California Medical Association and an associate member of the American Medical Association.

Hayden, Ralph Orville, San Jose. Died January 6, 1975 of heart disease, aged 68. Graduate of the University of Minnesota Medical School, Minneapolis, 1934. Licensed in California in 1941. Dr. Hayden was a member of the Santa Clara County Medical Society.

Helming, Oscar C., jr., Napa. Died June 8, 1975 in Napa of cancer, aged 69. Graduate of Northwestern University Medical School, Chicago, 1932. Licensed in California in 1940. Dr. Helming was a member of the Napa County Medical Society.

Herrman, Albert J., Pacific Grove. Died April 10, 1975 in Monterey of cancer, aged 69. Graduate of the University of Michigan Medical School, Ann Arbor, 1934. Licensed in California in 1939. Dr. Herrman was a member of the Monterey County Medical Society.

Hidey, Robert M., Palos Verdes Estates. Died May 12, 1975 in Torrance of heart disease, aged 52. Graduate of New York Medical College, New York, 1948. Licensed in California in 1952. Dr. Hidey was a member of the Los Angeles County Medical Association.

Leary, William Gordon, jr., Aptos. Died June 15, 1975 in Aptos, aged 54. Graduate of the University of Virginia School of Medicine, Charlottesville, 1943. Licensed in California in 1946. Dr. Leary was a member of the Santa Cruz County Medical Society.

Livingston, Afton Munk, La Jolla. Died May 23, 1975 in La Jolla, aged 72. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1930. Licensed in California in 1947. Dr. Livingston was a member of the San Diego County Medical Society.

MacColl, Douglass R., Los Angeles. Died April 23, 1975 in Los Angeles of congestive heart disease and respiratory failure, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Dr. MacColl was a member of the Los Angeles County Medical Association.

NELSON, ALBERT E., Los Angeles. Died May 4, 1975 in Los Angeles of cerebral accident and arteriosclerosis, aged 82. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1928. Licensed in California in 1928. Dr. Nelson was a member of the Los Angeles County Medical Association.

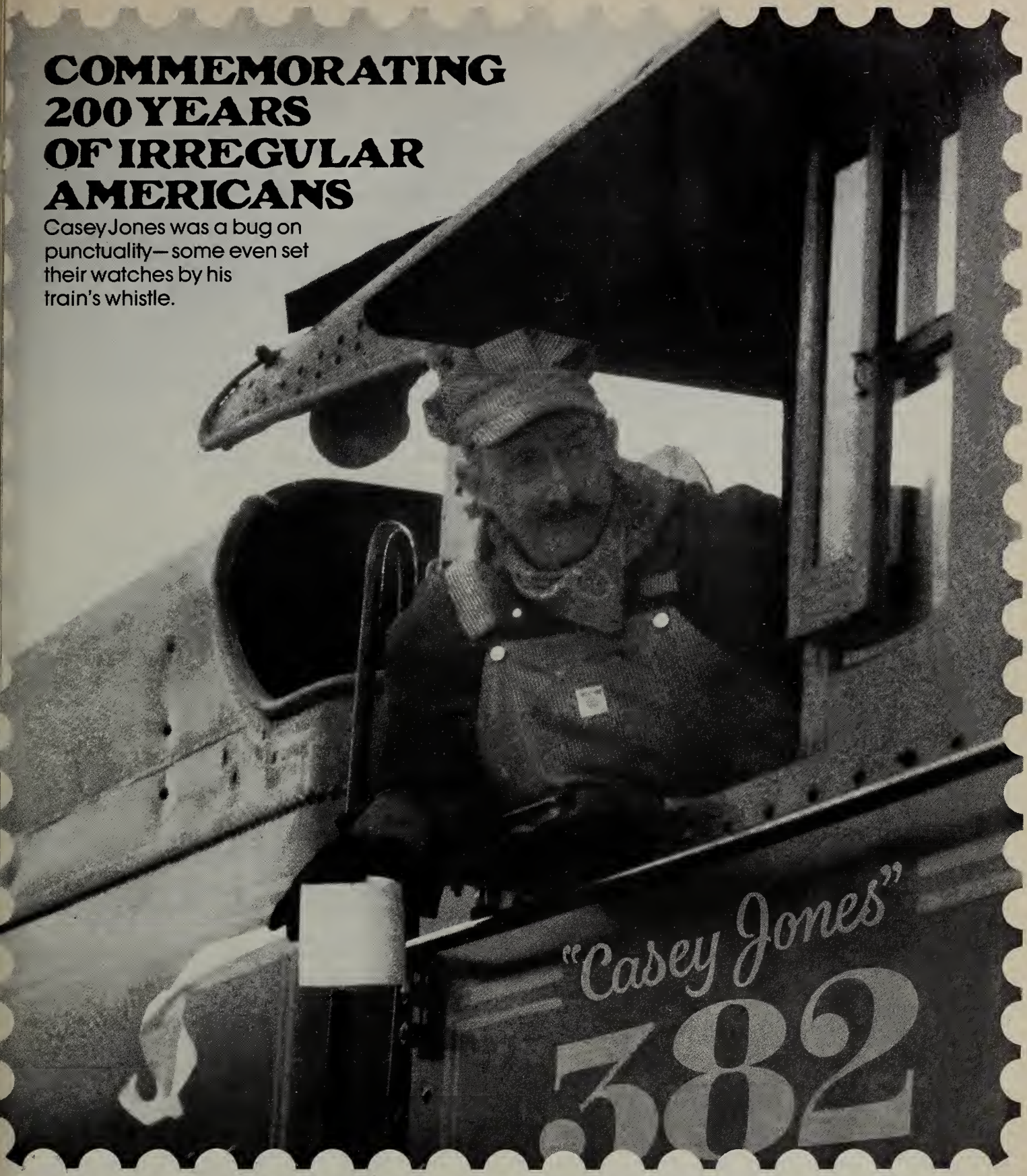
REEVES, WILLIAM ROLLIN, Salinas. Died January 3, 1975 of carcinoma of the pancreas and a cerebrovascular accident, aged 86. Graduate of Vanderbilt University School of Medicine, Nashville, 1912. Licensed in California in 1912. Dr. Reeves was a member of the Monterey County Medical Society.

SANDERSON, GEORGE H., Stockton. Died June 3, 1975 in Stockton, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Sanderson was a member of the San Joaquin County Medical Society.

SHERRICK, JOHN WESLEY, Oakland. Died June 20, 1975 in Oakland of carcinoma of the prostate, and cardiac failure, aged 88. Graduate of the University of Michigan Medical School, Ann Arbor, 1915. Licensed in California in 1922. Dr. Sherrick was a retired member of the Alameda-Contra Costa Medical Association.

SMITH, LAWRENCE WILLIS, Los Angeles. Died March 21, 1975 in Los Angeles of heart disease, aged 74. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1926. Licensed in California in 1929. Dr. Smith was a retired member of the Los Angeles County Medical Association.

ZAROWITZ, DANIEL G., Angelus Oaks. Died May 24, 1975 in Angelus Oaks of acute coronary occlusion caused by cardiac arrhythmia, aged 57. Graduate of Philadelphia College of Osteopathy, Philadelphia, 1949. Licensed in California in 1950. M.D. degree from California College of Medicine, 1962. Dr. Zarowitz was a member of the Los Angeles County Medical Association.



COMMEMORATING 200 YEARS OF IRREGULAR AMERICANS

Casey Jones was a bug on punctuality—some even set their watches by his train's whistle.

Just get me to the station on time. For 200 years, Americans have been in a hurry. But some things just don't happen on schedule—like bowel movements in a constipated patient. And for 200 years, Americans have dealt with this problem in a variety of ways—and with varying degrees of success.

Now there's Modane.® One tablet with the evening meal provides comfortable laxation in the morning...for postoperative, pregnant, or geriatric patients. Because it's **reliable.** Because it's **predictable.** Because it's **gentle.**

MODANE®

LAXATIVE TABLETS

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

CANCER

August 21-22—**Multidisciplinary Approach to Cancer Treatment.** UCSF at Children's Hospital, San Francisco. Thursday-Friday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** See Radiology and Pathology, September 27-28.

October 8—**Carcinoma of the Kidney, Adrenal, Retroperitoneum and Penis—3rd Annual Los Angeles Urological Cancer Conference.** L.A. Urological Society and American Cancer Society, Calif. Division, at Sheraton Hotel, Los Angeles Airport. Wednesday. Contact: William H. Tanner, ACS, 2932 Wilshire Blvd., Santa Monica 90403. (213) 828-7474.

MEDICINE

September 5-6—**San Diego County Heart Association—25th Annual Symposium.** Friday-Saturday. 13 hrs. $20, members; $25, non-members. Contact: Cathy Ware, Prog. Dir., SDCHA, 3640 5th Ave., San Diego 92103. (714) 291-7454.

September 12-13—**Occupational Hearing Conservation Workshop.** See Of Interest To All, September 12-13.

September 12-14—**Practical Approaches to Arthritis.** UCI at Marriott Hotel, Newport Beach. Friday-Sunday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18-June.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 18 hrs. $25.

September 26-27—**Infectious Disease—8th Annual Fall Meeting.** Children's Hospital of Oakland at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Calori, Medical Staff Office, Children's Hospital Medical Center, Oakland 94609. (415) 654-5600.

September 27—**Cardiovascular Disease—19th Annual Symposium.** American Heart Assn., Santa Barbara and San Luis Obispo Counties Chapter; Ventura County Heart Assn. at University Center, UC, Santa Barbara. Saturday. Contact: Judith Browning, Exec. Dir., AHA, Santa Barbara and San Luis Obispo Counties Chapter, P.O. Box 1071, San Luis Obispo 93406. (805) 544-1505.

September 27-28—**Workshop in Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 1-3—**San Francisco Heart Association—45th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. 18 hrs. $50. Contact: Evelyn Berggren, San Francisco Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 1-4—**Laboratory Advance in Internal Medicine.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

October 3—**Kidney Foundation of Northern California—Symposium.** Hyatt Union Square, San Francisco. Friday. Contact: Michael H. Humphreys, MD, Prog. Chr., Kidney Foundation of No. Calif., UC Renal Center, S. F. General Hospital, Bldg. 100, Rm., 350, San Francisco 94110.

October 3-4—**Cardiology Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley C. Gach, Coord., So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 4—**Hypertension.** USC. Saturday.

October 4—**Gastroenteritis.** Childrens Hospital of Orange County, Orange. Saturday. Contact: Merl J. Carson, MD, Med. Dir., CHOC, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 8—**Newer Concepts in Hypertension.** West Hills Hospital, Canoga Park. Wednesday. Contact: Continuing Medical Education, West Hills Hospital, 7300 Medical Center Dr., Canoga Park 91307. (213) 884-7060.

October 9-12—**California Society of Internal Medicine.** Vacation Village, San Diego. Thursday-Sunday. Contact: Carol H. Handley, Exec. Dir., SCIM, 1412 Central Towers, 703 Market Street., San Francisco 94103. (415) 362-1548.

October 10—**Current Trends in Dermatologic Therapy.** PMC. Friday.

October 10-11—**Controversies in Congenital Heart Disease.** The Earl and Loraine Miller Children's Hospital Medical Center and Long Beach Heart Assn. at Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. $125. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 15-18—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Saturday.

October 15-19—**American Association for Clinical Immunology and Allergy.** Riviera Hotel, Palm Springs. Wednesday-Sunday. Contact: Howard Silber, AACIA, P.O. Box 912, DTS, Omaha, Neb. 68101. (402) 558-5345.

October 18-19—**Dermatologic Surgery.** See Surgery, October 18-19.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** See Of Interest To All, October 18-19.

October 24-25—**Symposium on Respiratory Care.** Fresno Community Hospital. Friday-Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

October 26-30—**American College of Chest Physicians—41st Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Thursday, Contact: Alfred Soffer, MD, Exec. Dir., ACCP, 911 Busse Highway, Park Ridge, Ill. 60068. (312) 698-2200.

MENTAL RETARDATION

October 30-31—**Mental Retardation.** USC. Thursday-Friday.

OBSTETRICS AND GYNECOLOGY

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 25—**Non-Traditional Sexually Transmitted Diseases.** See Of Interest To All, September 25.

September 25-27—**Fall Symposium in Obstetrics and Gynecology—Oncology, Endocrinology and Infertility.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

September 27-October 4—**Workshops in Gynecologic Oncology, High Risk Pregnancy and Endocrinology-Infertility.** UCSF at Maui, Hawaii. One week.

October 4—**Office Gynecology.** PMC. Saturday.

October 5-10—**Pacific Coast Obstetrical and Gynecological Society.** Pebble Beach. Sunday-Friday. Contact: Melvin W. Breese, MD, 1133 SW Market St., Portland, Ore. 97201.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

October 8-10—**Fetal Monitoring.** USC. Wednesday-Friday.

October 15-19—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 31 hrs. $15 for members; $25, non-members. Contact: Ms. Dee Davis, Exec. Sec., PCFS, 5410 Wilshire Blvd., Suite 600, Los Angeles 90036. (213) 937-5514.

October 20-24—**Ob/Gyn Review.** USC. Monday-Friday.

October 24-25—**Perinatal Neurology.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday.

October 31—**Advances in Gynecology.** Northern California Ob-Gyn Society at Sacramento. Friday. Contact: Solon Barbis, MD, 1816 Professional Dr., Sacramento 95825.

PEDIATRICS

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 24-25—**Brennemann Memorial Lectures—32nd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 4—**Gastroenteritis.** See Medicine, October 4.

October 10-11—**Controversies in Congenital Heart Disease.** See Medicine, October 10-11.

PSYCHIATRY

September 20—**Psychotherapy.** UCD, Central California Psychiatric Society and Fresno County Dept. of Mental Health at Rodeway Inn, Fresno. Saturday. Contact: Central Calif. Psych. Society, 451 Parkfair Dr., Suite 4, Sacramento 95825. (916) 488-4320.

October 7-28—**Introduction to Behavioral Medicine.** UCLA. Tuesday evenings.

RADIOLOGY AND PATHOLOGY

September 20—**Nuclear Medicine Symposium — Imaging the Head.** Nuclear Medicine Section of Memorial Hospital Association at Holiday Inn (1612 Dale Road, on U.S. 99), Modesto. Saturday. No fee. Contact: Darrell K. Oberg, MD, 600 Coffee Rd., Modesto 95355. (209) 524-1211.

September 27—**Current Topics in Diagnostic Radiology.** Southern California Permanente Medical Group at Marriott Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 27-28—**Nuclear Medicine.** UCLA. Saturday-Sunday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** UCLA. Saturday-Sunday.

October 8-12—**American Society of Therapeutic Radiologists.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Sheila McGing, Exec. Sec., ASTR, 20 N. Wacker Dr., Room 2920, Chicago, Ill. 60606.

October 20-24—**Pathology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

SURGERY AND ANESTHESIOLOGY

August 17-29—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 3-November 19—**Acupuncture for Control and Management of Musculo-Skeletal Pain.** UCLA. Wednesday evenings.

September 6-13—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 7-19—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 2130 W. 3rd St., Los Angeles 90057.

September 8-12—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

September 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Thursday evenings. Contact: Linda Alperstein, Coordinator, Cont. Med. Ed., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

September 27-28—**American Society of Anesthesiologists—Regional Refresher Course.** Disneyland Hotel, Anaheim. Saturday-Sunday. 8 hrs. $50. Contact: John S. Hattox, Jr., MD, ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

September 27-28—**Workshop in Dermatologic Surgery.** See Medicine, September 27-28.

September 28-October 1—**Western Neurosurgical Society.** Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Wednesday. Contact: John S. Tytus, MD, 1118 9th Ave., Seattle 98101. (206) 223-6641.

October 8—**Carcinoma of the Kidney, Adrenal, Retroperitoneum and Penis—3rd Annual Los Angeles Urological Cancer Conference.** See Cancer, October 8.

October 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 11-12—**Current Clinical Status of Hyperbaric Oxygen.** UCSF. Saturday-Sunday.

October 13-17—**American College of Surgeons—Clinical Congress.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: C. Rollins Hanlon, MD, 55 E. Erie St., Chicago, Ill. 60611.

October 18-19—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 21-December 2—**Surgical Anatomy and Surgery.** USC. Tuesdays.

October 24-25—**Retinal Symposium.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

October 26-30—**Western Orthopedic Association.** Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. Contact: H. Jacqueline Martin, Exec. Sec., WOA, 1970 Broadway, Suite 1235, Oakland 94612. (415) 893-1257.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

August 17-21—**American Society for Pharmacology and Experimental Therapeutics.** UCD. Sunday-Thursday. Contact: Dr. Keith F. Killam, Jr., Chr., Dept. of Pharmacology, UCD. (916) 752-3421.

(Continued on Page 38)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known colorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, $T_3{}^{131}I$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Instructions for Use. The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

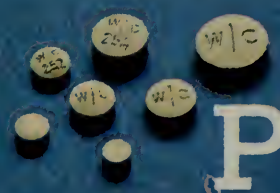
CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
Supplied. ¼ grain tablets in bottles of 100 (N0047-0250-51) and 1000 (N0047-0250-60); ½ grain tablets in bottles of 100 (N0047-0251-51) and 1000 (N0047-0251-60); scored 1 grain tablets in bottles of 100 (N0047-0252-51) and 1000 (N0047-0252-60); 1½ grain tablets in bottles of 100 (N0047-0253-51) and 1000 (N0047-0253-60); scored 2 grain tablets in bottles of 100 (N0047-0257-51); 3 grain tablets in bottles of 100 (N0047-0254-51) and 1000 (N0047-0254-60); scored 5 grain tablets in bottles of 100 (N0047-0255-51) and 1000 (N0047-0255-60). Full information is available on request. P-GP-51 4/c

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, N.J. 07950

Improving on nature...
from the rough, uncut stone
to the finished gem



In thyroid therapy, too...
all the qualities of the "natural" with the
added improvements of man...

Proloid®
(thyroglobulin)

natural thyroid...but uniquely purified
Devoid of any glandular debris.

natural thyroid...but triply standardized
Standardized chemically, biologically, and (at intervals) clinically, for consistent metabolic activity from batch to batch.

natural thyroid...but consistently fresh
Potency undiminished for up to 4 years under proper storage conditions.

It all adds up to natural thyroid with the added improvements of man.

Please see adjoining column for brief summary of prescribing information.

(Continued from Page 36)

August 20-24—**Family Practice Refresher Course—2nd Annual.** UCLA and Santa Monica Medical Center. Wednesday-Sunday.

August 24-29—**Family Practice Refresher Course—3rd Annual.** UCD. Sunday-Friday.

August 27—**Occupational Medicine Today.** Harbor General Hospital, Torrance. Wednesday. 7 hrs. $45. Contact: Ellen Woolfson, Cont. Ed. Coordinator, Harbor General Hospital, 1124 W. Carson A-19, Torrance 90502. (213) 775-7711, ext. 1373.

September 2-7—**Family Practice Review Course—6th Annual.** UCI at Newporter Inn, Newport Beach. Tuesday-Sunday.

September 3-November 19—**Acupuncture for Control and Management of Musculo-Skeletal Pain.** See Surgery, September 3-November 19.

September 9-October 28—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland Hospital. Tuesday evenings.

September 12-13—**Occupational Hearing Conservation Workshop.** PMC. Friday-Saturday. 20 hrs. $160.

September 14-19—**Emergency Medical Care Review.** UCD at Pajaro Dunes. Sunday-Friday.

September 15-19—**New Ways to Foster Health and Human Well-Being.** Health Training Resources Center, California Dept. of Health, at 1625 Shattuck Ave., Berkeley. Monday-Friday. Contact: Health Training Resources Ctr., Calif. Dept. of Health, 2151 Berkeley Way, Berkeley 94704.

September 18-19—**Experimental Approaches to the Study on Manipulation Therapy.** UCI at Center for Health Education, Long Beach. Thursday-Friday.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** See Medicine, September 19-20.

September 22-26—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

September 23-November 25—**Yoga: Clinical Applications and Techniques.** UCLA at 1620 Preuss Rd., W. Los Angeles. Tuesday, 7:30-10:00 p.m. 25 hrs. $85.

September 25—**Non-Traditional Sexually Transmitted Diseases.** VD Controllers, CMA VD Task Force at San Francisco Medical Society, San Francisco. Thursday. Contact: Erwin Braff, MD, S. F. Co. Health Dept., 101 Grove St., Room 307, San Francisco 94102. (415) 558-4877.

September 30-December 16—**Bedside Clinics.** USC. Tuesdays.

October 2-4—**Western Occupational Medical Association.** Sheraton Harbor Isle, San Diego. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 3-4—**Recent Trends in Management of Obesity.** UCSD. Friday-Saturday.

October 5-10—**American Physiological Society—26th Annual Fall Meeting.** Sheraton-Palace, San Francisco. Sunday-Friday. Contact: Mrs. Helena B. Lemp, APS, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-7010.

October 6-10—**Primary Care.** STAN. Monday-Friday.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** San Francisco General Hospital (7th) and UCSF (8th). Tuesday-Wednesday. Visiting professor will be D. J. Weatherall, MD, Radcliffe Infirmary, Oxford, England. October 7—**Molecular Pathology of the Thalassaemia Disorders.** October 8—**Clinical and Genetic Aspects of the Control of Foetal Haemoglobin Production.** Contact: Susan Nutter, S.F. General Hospital, 1001 Potrero Ave., San Francisco 94110. (415) 648-8200, ext. 404.

October 8-11—**Medical Society of the United States and Mexico—23rd Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: Virginia E. Bryant, Exec. Sec., 333 W. Thomas Rd., Suite 207, Phoenix, Ariz. 85013.

October 9-11—**Wound Healing—Theory and Practice.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

October 9-30—**What to Tell Your Patients When They Ask About Acupuncture, Biofeedback and Hypnosis.** UCLA. Thursdays.

October 10—**American Geriatrics Society, Inc., Western Division—4th Annual Meeting.** Newporter Inn, Newport Beach. Friday. $35. Contact: Irving Hirshleifer, MD, 1080 N. Indian Ave., Palm Springs 92262. (714) 325-5044.

October 16-17—**Immunology for the Practicing Physician.** UCSF at Kaiser Center Auditorium, 300 Lakeside Dr., Oakland. Thursday-Friday.

October 17—**Antiplatelet Drugs and Thrombosis.** PMC at Miyako Hotel, San Francisco. Friday.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

October 18-19—**Review of Antimicrobial Therapy.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201;

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

August 15-16—**John Tomlin Memorial Cancer Lectures.** Medford. Contact: American Cancer Society, Oregon Division, Inc., Jackson County Unit, P.O. Box 698, Medford 97501, phone (503) 779-6091.

Sept. 10-14—**Oregon Medical Association Scientific Session and House of Delegates.** Portland, Hilton Hotel. Contact: James A. Kronenberg, Oregon Medical Association, 2164 S. W. Park Place, Portland 97205, phone (503) 226-1555.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

September 3-5—**Western Conference of the American Lung Associations.** Wednesday-Friday. Olympic Hotel, Seattle. Contact: Janet Chalupnik, Washington Lung Association, 216 Broadway E., Seattle 98102. (206) 329-4411.

September 8-10—**Topics in Clinical Microbiology.** Monday-Wednesday. Univ. of Wash. Health Sciences Center, Seattle. 9 hrs., $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 10-12—**Recent Advances in Infectious Diseases—American College of Physicians.** Wednesday-Friday. Olympic Hotel, Seattle. 16 hrs. Members, FACP $100; non-members, $150; ACP Associates, $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

The 2 most widely prescribed sodium levothyroxine (T_4) products are:

LETTER®
(Sodium levothyroxine, Armour) Tablets

SYNTHROID®
(Sodium levothyroxine) Flint Tablets

LETTER® IS 10% LOWER IN PRICE THAN SYNTHROID®*

Armour Pharmaceutical Company
Phoenix, Arizona 85077

*Armour's published list price to pharmacies for LETTER is 10% less than the Flint published price for Synthroid in bottles of 100 of the same strength. Pharmacy charges to the patient will vary from pharmacy to pharmacy, depending on individual locations, policies and services offered.

September 12-13—**American College of Physicians Regional Meeting with Washington State Society of Internal Medicine.** Friday-Saturday. Olympic Hotel, Seattle. 5½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 14-17—**North Pacific Pediatric Society Annual Meeting.** Sunday-Wednesday. Rosario, Orcas Island, Washington. Contact: Bernard P. DeJong, MD, Secretary, 3195 Granville St., Vancouver 9, B.C., Canada. (604) 738-2102.

September 15-16—**Liver and Cancer.** Monday-Tuesday. Univ. of Wash. Health Sciences Center, Seattle. 19 hrs. Fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 17-19—**Physical Therapy Training Institute.** Wednesday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 19-22—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan Knudson, Exec. Director, 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110.

September 26-27—**Arthritis Days '75.** Friday-Saturday. Olympic Hotel and Univ. of Wash. Health Sciences Center, Seattle. 9 hrs. Fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 26-27—**Review of Basic OB-GYN.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Div. of CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 1-June 9, 1975—**Internal Medicine Review.** Wednesday evenings, 6 p.m.-8 p.m., 35 weeks. Univ. of Wash. Health Sciences Center, Seattle. 70 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 2-4—**Montana State Medical Association Annual Meeting.** Thursday-Saturday. Fairmont Hot Springs Resort, Gregson, Montana. Contact: G. Brian Zins, Exec. Director, 2021 11th Ave., Suite 12, Helena, MT 59601.

October 4-5—**Skin Surgical Techniques.** Saturday-Sunday. Univ. of Wash. Health Sciences Center, Seattle. Limited to 50. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (296) 543-1050.

October 13-17—**Treating the Untreatable—Univ. of Washington School of Medicine's Eastern Washington Circuit Course.** Pullman, 13; Walla Walla, 14; Tri-Cities, 15; Yakima, 16; Wenatchee, 17. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 14-19—**American Society of Clinical Hypnosis Annual Meeting.** Tuesday-Sunday. Washington Plaza Hotel, Seattle. Contact: Ernest T. Guy, Exec. Director, East Devon Ave., Suite 218, Des Plaines, IL 60018. (312) 297-3317.

October 16-17—**Team Effort in the Management of Cancer.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 17-18—**Washington State Heart Association Symposium.** Friday-Saturday. Olympic Hotel, Seattle. Fee to be determined. Contact: De Loris Savage, R.N., Wash. State Heart Assoc., 333 1st Ave. W., Seattle 98119. (206) 285-2415.

October 30-31—**Office Management of Chronic Pain.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 6-7—**Learning Disabilities: Dilemma and Discussion.** Thursday-Friday—Univ. of Wash. Child Development and Mental Retardation Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir., CME, E-305, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 13-14—**Current Concepts in Drug Therapy.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours to be determined. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

Index to The Western Journal of Medicine Advertising

Armour Pharmaceuticals Co.
Letter 39

Ayerst Laboratories
Premarin 8, 9

Boehringer Ingelheim Ltd.
Combipres 11, 12, 13, 14, 15, 16

Burroughs Wellcome Co.
Neosporin Ointment 25
Empirin Compound with Codeine 29

Classified 26, 32

Compton Foundation 26

Eli Lilly & Company, Inc.
Manufacturer of Darvocet-N 100 & Darvon Compound-65 24

Merck Sharp & Dohme
Triavil 18, 19, 20

Pharmaceutical Manufacturers Association 30, 31

Presto Food Products Inc.
Mocha Mix ..... 3rd Cover

Roche Laboratories
Dalmane ..... 2nd Cover and Page 1

William H. Rorer Inc.
Camalox 4, 5
Maalox ..... 4th Cover

W. B. Saunders Company 21

G. D. Searle & Co.
Pro-Banthine 28, 29

Smith, Kline & French Co.
Dyazide 3

Stanford University School of Medicine
Primary Care/Intensive Care Program 17

The Upjohn Company
Dulin Research 6, 7

Warner Chilcott Laboratories
Proloid 36, 37

Warren-Teed Pharmaceuticals Inc.
Modane 33

Westwood Pharmaceuticals Inc.
Pre-SUN 10

Wyeth Laboratories
Bicillin/Wycillin 22, 23

Refer to: U Hoi Sang, Wilson CB; Surgical treatment of intracranial vascular malformations. West J Med 123:175-183, Sep 1975

THE WESTERN
Journal of Medicine

Surgical Treatment of Intracranial Vascular Malformations

HOI SANG U, MD, *and* CHARLES B. WILSON, MD, *San Francisco*

Arteriovenous malformations often pursue a progressive course, increasing in morbidity and mortality. Whenever possible they should be excised totally. The operating microscope, bipolar coagulation and high quality angiography have extended the generally accepted indications for surgical operation. Intraoperative adjuncts of contrast angiography and cardiac green have been helpful in accurately defining deep or complex lesions.

CEREBRAL ARTERIOVENOUS MALFORMATIONS (AVM's) were first described by Steinheil in 1895. Although classified as tumors (angiomas) by Cushing and Bailey[1] and Dandy,[2,3] subsequent observations established their congenital and nonneoplastic nature.[4-6] In the preangiography era, the study of AVM's was confined to the operating table and to the postmortem examination. The introduction of angiography by Egas Moniz (1927) provided a means of studying their dynamic and anatomical characteristics. Clinical and angiographic evaluation of patients harboring AVM's has established their liability for expansion, repeated hemorrhage and seizures with associated morbidity and mortality. In 1948, Olivecrona[7] predicted that conservative management would be ineffective in treating AVM's, a projection that was subsequently confirmed by the disappointing long-term results reported by Moody and Poppen,[8] Forster[9] and Morello.[10] The nature of the AVM was well expressed by Potter,[11] who anticipated the futility of carotid ligation, decompression and clipping of feeding arteries in long-term treatment. At best, these procedures provide temporary palliation because the AVM is not eliminated. The treatment of choice is total excision, when possible, as dictated by the lesion's location and size.

Our approach to the treatment of arteriovenous malformations reflects the current aggressive attitude expressed by many neurosurgeons. Advancements in angiography and surgical technology have broadened the indications for surgical treatment of these anomalies, and our purpose here is to present the results of treating 31 patients harboring AVM's, many of which were considered unsuited for operation before the introduction of surgical microscopy.

Clinical Material

This study comprises 31 patients treated by one surgeon (C.W.) on the Neurosurgical Service of the University of California Medical Center, San Francisco, during the period from 1968 to 1974 (Table 1).

During the period covered by this study an equal number of patients did not meet our criteria for operation, the majority because of either large size or location of AVM's, or both. In most instances these latter patients were referred by other neurosurgeons who had considered these malformations inoperable because of anticipated surgical morbidity and mortality. Because of re-

From the Department of Neurological Surgery, University of California, San Francisco.

This work was supported in part by NINDS Training Grant 5593.

Submitted January 28, 1975.

Reprint requests to: C. B. Wilson, MD, Department of Neurological Surgery, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

TABLE 1.—*Treatment of 31 Patients with Cerebral Arteriovenous Malformation*

Site	*Patient*	*Age*	*Sex*	*Size and Location*	*Manifestation*	*Preop Status*	*Procedure*	*Discharge Status*	*Follow-Up Status*
Left temporal lobe ..	1	28	M	Small, posterior temporal lobe	2d of left temporal headache, memory loss	Receptive and dysnomic aphasia, mild Gertsman's syndrome	Excision; evacuation of intracerebral hematoma	Very mild aphasia	No residual, fully employed (6 years)
	2	58	F	Large, undersurface temporal lobe	Bifrontal and occipital HA; forgetfulness, incoordination right hand × 1 month	Inappropriate affect, left sided ataxia	Ligation of feeding vessels	Mild HA, mild incoordination and unsteadiness, arteriographic decrease in size of AVM	Same as discharge (5 years)
Left occipital lobe ...	3	35	M	Large, superficial and deep occipitoparietal	Seizure (focal R and general) × 16 years, SAH 47d preop, clipping of some feeders 30d preop	Right homonymous hemianopia	Excision; expired at operation, 2° cardiac arrest	....	....
	4	21	M	Moderate, medial left occipital	SAH and intraventricular H with resultant hydrocephalus treated with VP shunt 6m preop	mild recent memory decrease	Excision with ligation of left posterior cerebral artery under hypothermia	Right hemianopia	Significant improvement in right hemianopia, some lack of awareness of time (1 year), fully employed, intellectually active
Left parietal	5	53	F	Small, superficial	Hemorrhage; confusion; dysphasia; personality change × 2 weeks	Right homonymous hemianopia; anomic and receptive aphasia	Excision; evacuation of intracerebral hematoma	Mild anomic dysphasia	Considerable improvement of aphasia (7 months)
	6	25	F	Small, midparietal, deep	Episodes of shaking right side with syncope and dysphasia × 3 weeks	Disoriented; poor memory; dysphasia; right hemiparesis	Excision; evacuation of hematoma	Mild dysphasia and right hemiparesis	Normal exam. (4 months), fully employed
	7	28	F	Small, subcortical	Dysphasia; grand mal seizure 10m; headache 10m	Neurologically intact	Excision with intraop. arteriogram and hypothermia	No deficit	No deficit; normal activity (4 months)
	8	36	M	Moderate, intraventricular	SAH 7 years ago, treated with clipping of feeding vessels; re-SAH 2 weeks preop	Moderate meningismus; neurologically intact	Excision with clipping of PCA	Right hemiparesis, dysphasia	Minimal dysphasia, improved hemiparesis, grand mal seizure × 2 in past 2 years (2 years)
Left frontal lobe	9	16 months	M	Small, antero-lateral Sylvian	SAH, seizure, coma, flaccidity × 21d	Coma responding to deep pain; anisocoria L>R, spastic quadraplegia	Clipping of left MCA with observed good filling of arterioles over cortex	Irritable, questionable blindness, spastic quadraparesis	Retarded with residual motor weakness (2 years)
	10	46	M	Large, superficial	Straining→nausea, vomiting, confusion, dyscalculia 2m F.U.A.	Hesitant speech, dys- memory and compre-	Clipping of feeding showed decreased size	No change	Working, neurologi-

				frontal	years				year)
Right occipital lobe ..	12	25	M	Moderate, medial	SAH, 11d preop	Left homonymous hemianopia	Resection; drainage of hematoma	Pronounced improvement of visual field, A/G showed residual AVM requiring second operation for removal; continuous improvement	Very mild visual field defect, back in school (5 months)
	13	19	F	Small, at occipital pole	Intracerebral hemorrhage with left hemianopia	Left homonymous hemianopia with visual hallucination	Excision; evacuation of hematoma	90 percent recovery of visual field	Back in school, playing tennis, asymptomatic (6 months)
	14	49	M	Extensive, mixed pialdural AVM of occipitotemp region	Grand mal seizure 9 years before, followed by SAH; disorientation, difficulty in gait and speech × 8 w	Awake, responsive to pain, mute, ? visual capacity, profound quadriparesis	Clipping of PCA and feeding vessels in 2 sessions	Alert, awake, verbalizes, moving all extremities, ambulates, left hemianopia	Continues to improve, intellectually intact, ambulatory, capable of self care (4 months)
Right parietal lobe ..	15	21	F	Large, deep	SAH 4 years prior, seizure with left hemiparesis 3 months prior; SAH with left hemiplegia and obtundation 1 month preop	Left hemiparesis	Excision with hypothermia	Pronounced improvement of left hemiparesis	Working with minimal hemiparesis (1 year)
	16	25	F	Large, superficial	Focal seizures × 4 years, visual hallucinations × 1½ years, grand mal seizure followed by poor memory 17d preop	Left hemiparesis with decreased recognition of objects	Excision	Marked improvement of left hemiparesis	Minimal left hand weakness; without seizure (7 months)
	17	49	F	Huge, deep and superficial	Seizure × 6 years, SAH 3 years; unsteadiness with drop attacks from AVM steal syndrome × 5m	Clumsiness with unsteady gait and intellectual deterioration	Excision with hypothermia; unexplained hemorrhage into entire right hemisphere with herniation of brain out of craniotomy site	Coma complicated by cardiac arrest, hypoxia, stiff lung syndrome, septic shock, expired fourth postop day	....
	18	11	M	Moderate, deep	Sudden left hemiparesis with slow recovery × 5m; intracerebral hemorrhage with left hemiparesis × 36 hours	Lethargic, combative, left decerebration with hemiparesis; ? vision	Excision with removal of intravent clot	Awake, alert, appropriate; left hemianopia; markedly improved left hemiparesis	Residual left hemiparesis, in school (1 year)
	19	31	F	Small, deep	Left focal seizure × 2 years, left hemiparesis × 2 months	Left hemiparesis	Excision, hypothermia, intraop A/G	Pronounced improvement, left hemiparesis	Intact, full activity as mother and housewife (1 year)
Right frontal lobe ...	20	30	M	Small, internal capsule	SAH with left hemiparesis × 18 d	Lethargic, left hemiparesis	Obliteration; evacuation of hematoma	Minimal left hemiparesis	Intact except for 1 episode left focal seizure following alcohol abuse (1 year)

Site	Patient	Age	Sex	Size and Location	Manifestation	Preop Status	Procedure	Discharge Status	Follow-Up Status
Paramedian	21	16	F	Moderate, left frontal parasagittal	Generalized seizure × 10 years, self neglect	Intact	Excision; evidence of old hemorrhage found	Intact	Intact, pursuing college education without seizure (6 years)
	22	56	M	Small to medium, left parietal parasagittal	Transient right dysesthesia × 2 months	Intact	Excision; hypothermia	Mild weakness right leg	Improving right leg weakness (2 months)
	23	23	F	Small, right post frontal	Transient left hemiparesis 6 years preop; SAH with confusion and left leg weakness 20 d preop	Mentally more alert, left hemiparesis	Excision, evacuation of intracerebral hematoma	Clearing of left hemiparesis	Mild residual left hemiparesis (3 years)
	24	25	M	Small, rostrum corpus callosum	Intermittent frontal headaches; SAH with loss of consciousness 1 month preop	Bilateral leg weakness	Obliteration	Intact	Intact, working (1½ years)
	25	45	M	Small, left mid corpus callosum	Difficulty walking and moving right arm × 1 month	Right motorsensory impairment	Obliteration	Intact	Intact, working (1 year)
Orbital	26	58	M	Left sup and lateral orbit outside muscle cone	Reddening left eye progressive × 4 months, exophthalamus, diplopia, blurred vision, swelling	Axia protrusion peribulbar tissue; anteralized conjunctival veins; EOM 10-20 percent, diplopia all directions	Excision through craniotomy	Mild diplopia upward gaze	Normal (1½ years)
Posterior fossa	27	30	F	Small, right vert	Bruit after trauma, recurred after clipping feeders 1 year preop	Intact	Obliteration, clipping right vertebral artery	Intact	Intact, working (6 months)
	28	24	M	Small, right cerebellar hemisphere	SAH with vertigo 10 days preop	Aniscoria R>L, right VI nerve paresis with diplopia; right lateral gaze nystagmus	Excision, evacuation intracerebellar hematoma	Pronounced improvement of right VI nerve paresis, no subjective complaint	Intact, gainfully employed (6 years)
	29	39	F	Left PICA, small	Left tinnitus × 1 year, dysarthria × 1 w, severe occipital headache × 3d	Somnolent, left lateral gaze nystagmus	Excision	Improved tinnitus; no headache or dysarthria	Intact, occasional headache (5 years)
	30	17	F	Superior vermis, moderate	SAH 4 years; SAH 2 months with left sided incoordination	Left ataxia	Excision	Intact	Intact, in school (4 years)
	31	31	F	Left tonsil, small	Bifrontal headache × 6-7 years; SAH 2 months	Intact	Excision	Intact	Vertigo of unknown cause 4 weeks postop finally resolved (2 months)

A/G = angiography
AVM = arteriovenous malformation
d = day
EOM = extraocular movements
H = hemorrhage
HA = headache
L = left
m = month
MCA = middle cerebral artery
PCA = posterior cerebral artery
PICA = posterior-inferior cerebellar artery
PTA = prior to admission
R = right
Re-SAH = rebleeding of subarachnoid hemorrhage
SAH = subarachnoid hemorrhage
VP = ventriculo peritoneal
w = week

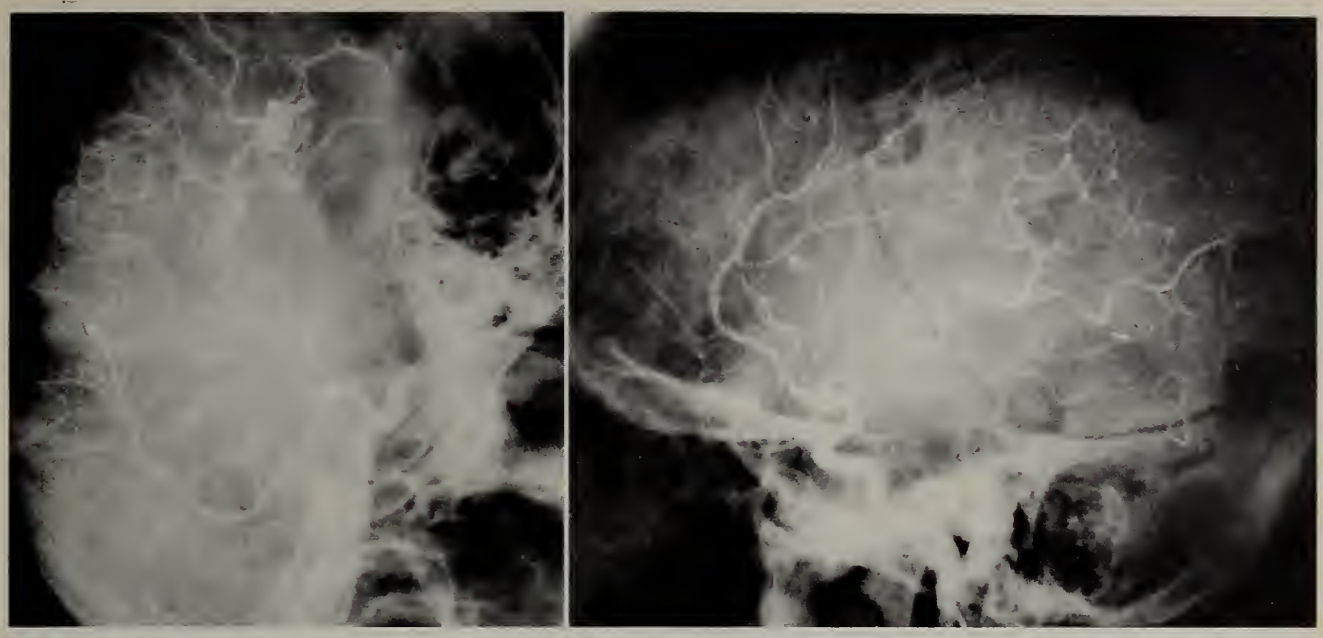


Figure 1.—(Case 7) **Left,** preoperative arteriovenous malformation (AVM) in the left parietal-occipital region. **Right,** postoperative excision of AVM.

ferral patterns our experience is heavily biased toward unfavorably situated lesions, and as a consequence the proportion of patients undergoing operation does not reflect the operability of AVM's in an unselected sample.

Twenty-nine cases were documented by angiography before operation. In two cases (6 and 20) the AVM presented as a mass, later identified at operation as hematoma secondary to an AVM. The surgical objective was excision or obliteration of the lesion, even when it was situated in crucial regions of the brain as in case 7 (Figure 1). This approach was modified for large malformations involving more than one third of a hemisphere (such as cases 2, 10 and 14). In one case (9), the patient was moribund from intracerebral hemorrhage, and surgical operation was undertaken as a palliative measure. In the patients in whom excision or obliteration of AVM's was done, postoperative arteriograms made in 18 cases confirmed successful elimination of the AVM as shown in Figures 2 and 3. In the remaining seven patients treated similarly, no angiogram was made after operation, either because the patient refused or because of total elimination of the AVM at operation and the unjustified risk of angiography. Patients in the latter group have been followed for two months; seven months; two, three, four, five and six years and in none has there been an indication for postoperative angiography.

Of the four patients treated with ligation of feeding arteries, two were studied postoperatively —and in both, the residual malformation was smaller.

Age at onset of symptoms ranged from 16 months to 58 years, and in one third (11 of 31) of patients initial symptoms developed in the third decade. The patients were distributed equally as to sex (16 and 15). Supratentorial AVM's predominated (25 of 31), with the greater number (15 of 25) occupying the right cerebral hemisphere.

In almost one half (14 of 31) of patients, intracranial bleeding was the initial symptom, at an average age of 21 years, and the majority of these (9 of 14) presented with an intracerebral hematoma. In one fourth (7 of 31) of patients, the initial symptom was a seizure, occurring at an average age of 35 years and typically focal. Only three patients had headache (in the absence of recognized bleeding) as an initial symptom. Two patients described sensory phenomena and two had disturbance of speech as the initial symptom. Single instances of motor deficit, visual deficit and a bruit account for the remainder.

Relationship of Symptomatic Hemorrhage and Epilepsy to Lesion Size

The malformations divide into three groups: small (less than 2 cm in overall diameter), moderate (2 to 4 cm in overall diameter) and large (greater than 4 cm in overall diameter). The smaller lesions tended to present with hemorrhage, while the large ones were more often associated with convulsions (Table 2).

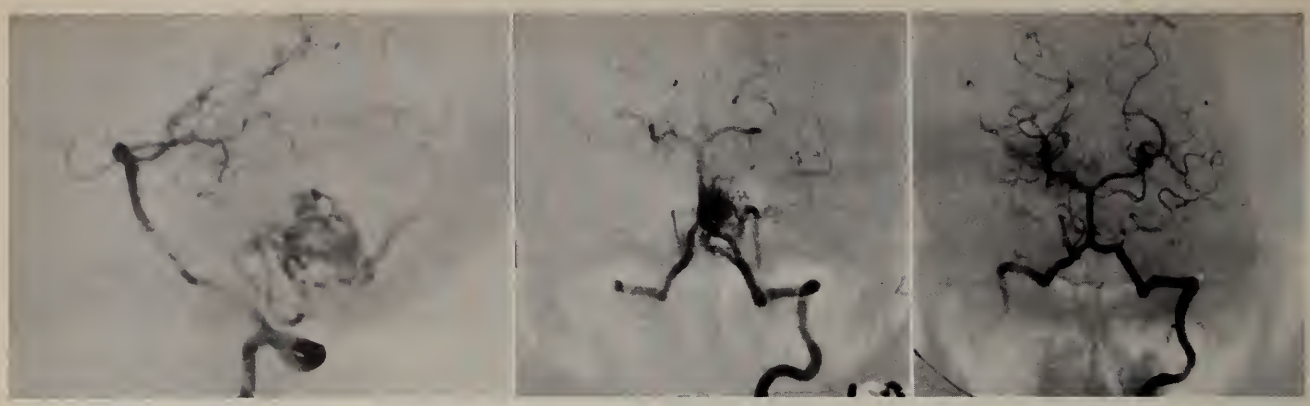


Figure 2.—(Case 13) **Left,** preoperative arteriovenous malformation (AVM) in the right occipital pole (note arterial supply from the anterior circulation). **Center,** preoperative AVM showing supply from the posterior circulation. **Right,** postoperative excision of AVM.

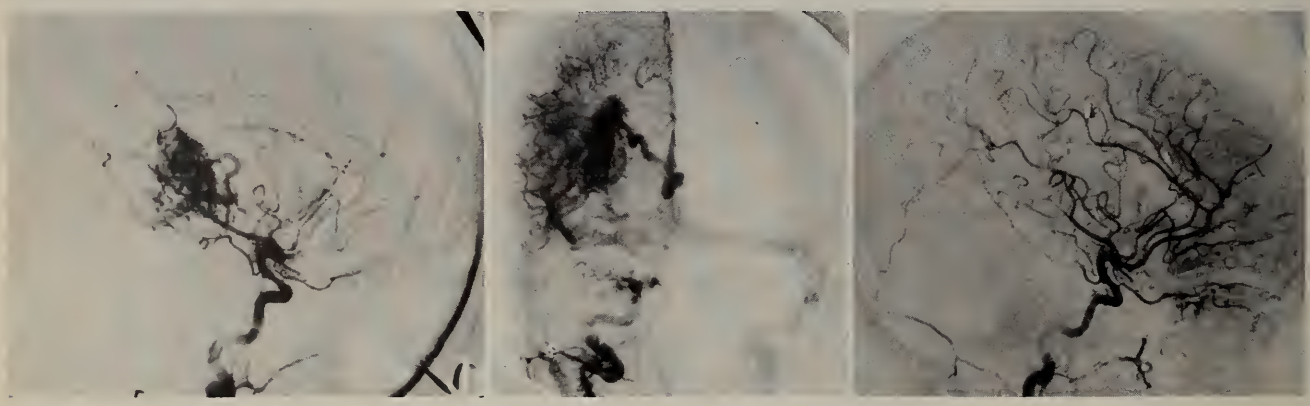


Figure 3.—(Case 18) **Left,** preoperative deep right parietal arteriovenous malformation (AVM) (lateral view). **Center,** preoperative deep right parietal AVM (anteroposterior view). **Right,** postoperative excision of AVM.

Diagnosis

In all patients, angiographic studies were done, and in 29 patients, the diagnosis of arteriovenous malformation was established conclusively. The remaining two patients presented with intracerebral hematomas; the diagnosis was made at surgical operation and confirmed by pathological examination.

Surgical Technique

Our goal was excision whenever possible, and the operating microscope was used in every case. Hypothermia—to approximately 31°C (87.8°F)—was used in four lesions, three of which were small or moderate in size, but located deep within the hemisphere. The fourth lesion was moderate in size and located in the dominant parasagittal parietal region. Exposure of deeply situated malformations necessarily promotes the development of postoperative cerebral edema, and in our opinion the lessened reactivity of hypothermic brain argues for the use of hypothermia in selected cases.

TABLE 2.—*Relationship of Symptomatic Hemorrhage and Epilepsy to Lesion Size*

	Small (17)	*Moderate (7)*	*Large (7)*
Hemorrhage	8 (47%)	5 (71%)	1 (14%)
Epilepsy	2 (12%)	1 (14%)	4 (57%)

Intraoperative arteriography and injection of cardiac green for identification of afferent vessels were used in three patients. Intraarterial injections were made through a catheter placed in the superficial temporal artery, directed into the external carotid artery and maintained with a constant infusion pump. For direct visualization of arteries contributing to the malformation, we injected a bolus of cardiac green (Cardiogreen®, Guth Pharmaceuticals), 10 to 20 ml, and in each instance this method provided satisfactory color contrast for identification of arteries leading into the shunt. In two patients the lesion's small size and deep location dictated the use of arteriography for localization with the help of cortical markers. In the third patient, the lesion was large and superficial; arteriography and cardiac green were used

for identifying afferent and efferent vessels in a feeder-clipping palliative procedure to ensure adequate reduction of the AVM. Hypotension was not used in any patient.

Mortality (Two Cases, 6.4 Percent)

One death early in the series resulted from uncontrolled intraoperative intraventricular bleeding that led to irreversible cardiac arrest. Removal of the AVM in this patient had been abandoned by another surgeon, and the patient was referred to us after recurrent bleeding. The second death resulted from immediate postoperative complications. In this patient there was massive intracerebral hemorrhage secondary to restoration of blood flow to a chronically ischemic cerebral hemisphere. Both deaths followed attempts to excise massive malformations.

Postoperative Condition (After Excision or Obliteration)

The majority of disabilities (about three quarters) were reversed by excision of the AVM, and about one fourth of the patients improved. New disabilities appeared in four cases. In the first case, a patient in whom there was a moderate-sized left medial occipital AVM, the operation included clipping of the posterior cerebral artery resulting in a right homonymous hemianopia, which subsequently showed pronounced improvement. In the second case a moderate-sized parasagittal left parietal AVM was excised, causing mild weakness in the patient's right leg. Two months after operation the weakness has resolved and the patient now walks without a limp. In the third patient, there was a moderate-sized left parietal lesion at the trigone, and postoperatively a transient right hemiparesis and dysphasia developed, with progressive improvement over two years. Grand mal seizures were also experienced, twice in two years; these are now under control. The fourth case (Figure 4) was that of a patient with a left cerebellar tonsillar lesion in whom unexplained positional vertigo developed four weeks postoperatively despite intact neurological status for the first two weeks after operation. This has now cleared completely.

Of the patients who had intracranial hemorrhage (14 cases), five patients have been followed from two to seven months, and the rest for one to six years; in none of these has bleeding recurred. In one patient, a single grand mal seizure occurred.

Of the patients presenting initially with epilepsy (six cases), followed from seven months to six years in four cases, none had recurrence of seizures. Two patients, in both of whom progressive neurological deterioration and repeated bleeding developed before surgery, were operative deaths.

Postligation of Feeding Vessels

Feeding vessels were ligated in four cases. After five years of followup, patient 2 has not shown significant improvement. Patient 9 was moribund and in coma before operation. Now at two years of age, he is retarded and severely incapacitated. Patient 10, three years postoperatively, has been asymptomatic and is working full time. Patient 14 was quadriparetic and mute before operation; she has improved sufficiently to resume preparing meals and keeping house. Mentation is intact and the patient has regained normal speech.

Postoperative Angiographic Evaluation

- Postexcision and obliteration group (25 cases). In 18 patients (72 percent), findings on postoperative angiographic evaluation showed complete obliteration of the AVM. Seven patients were not studied, and at this time none has had clinical symptoms requiring evaluation.
- Postligation of feeding vessels group (4 cases). In the two cases studied, AVM size decreased. Two cases were not studied following operation.

Follow-up Status (Table 3)

Twenty-nine patients have been followed for periods ranging from two months to six years (ten patients were followed for up to one year, nine patients for one to two years, two patients for two to three years, two patients for three to four years, one patient for between four and five years, and five patients for five to six years).

Table 3 compares preoperative to postoperative capacity. Before operation, 60 percent of patients were moderately to severely incapacitated, while only 29 percent were minimally, or not at all, incapacitated. Although the number of patients in the minimally incapacitated group did not increase postoperatively, the number of patients with full capacity increased; accordingly the number of patients with moderate to severe incapacity decreased.

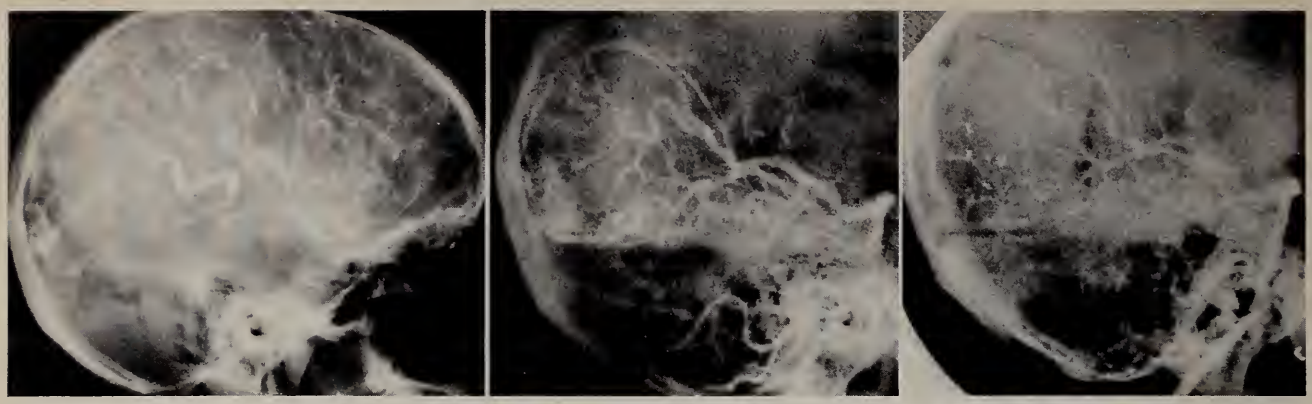


Figure 4.—(Case 31) **Left,** preoperative left cerebellar tonsillar arteriovenous malformation (AVM) (lateral view). **Center,** preoperative left cerebellar tonsillar AVM (Towns view). **Right,** postoperative excision of AVM.

TABLE 3.—*Working Capacity Before and After Surgical Operation*

Status	*Preoperative*	*Postoperative*
Full capacity	1	17
Incapacitation		
Light	8	7
Moderate	9	3
Severe	10	2
Coma	1	0
TOTALS	29	29

Full capacity: asymptomatic, no deficit, fully employed.

Incapacitation
Light: No symptoms to minimal symptoms, minimal deficit, fully employed.
Moderate: Mentally alert and independent, full self care, moderately symptomatic, has moderate motor or sensory deficit (for example, paresis), unemployed or partially employed.
Severe: Mentally confused, severe subjective complaints, severe motor or sensory deficit (for example, plegias), requiring care.

Discussion

In the present series, the majority of patients became symptomatic in the 20 to 40 year age group, a finding similar to that of Morello[10] and Paterson.[12] The distribution between male and female is equal in our group, although other authors have reported an increased incidence in males.[7,10,12] Presenting symptoms and their relative frequencies are also similar to those noted by Paterson.[12] Forster,[9] Henderson[13] and Morello[10] report hemorrhage as the more frequent presenting symptom, in as many as 75 percent of cases; although McKenzie[14] and Olivecrona[7] reported the greater prevalence of seizures. Smaller malformations bleed more frequently while the larger ones are more prone to manifest themselves by seizures, either focal or general.[10,12,15]

The natural history of AVM's is one of symptomatic recurrence with progressive disability especially in those that bleed.[9,12-14,16,17] Our patients 15 and 30 illustrate the point. Olivecrona stated, "In the end, probably most, if not all, patients die of hemorrhage or are completely incapacitated. Mental deterioration is a common feature in cases of an inveterate lesion."[7] According to the Cooperative Study,[12] the mortality from the initial hemorrhage is about 10 percent, the risk of a second hemorrhage is 20 percent with a mortality of 13 percent for the second hemorrhage and about 20 percent for subsequent hemorrhage. Potter[11] presented a plausible pathophysiological mechanism for recurrent bleeding and Waltimo[18] provided evidence that these malformations, when small, tend to enlarge. Presented with such an unfavorable natural history, there is no strong argument for conservative treatment.

Surgical treatment has taken the form of decompression, exploration, ligation of internal carotid artery and ligation of feeding vessels—as well as total excision or obliteration. Our experience with ligation of feeding vessels is limited and inconclusive. The results of surgical procedures other than total excision have been disappointing,[7-9,19-21] and most surgeons regard total excision as the treatment of choice.[7,9,10,16,19,21]

Traditionally indications for surgical operation have been: (1) repeated subarachnoid hemorrhage, (2) intracerebral hematoma and (3) progressive intractable neurological disability. To these indications we have added (1) malformation causing seizure without prior bleeding, if favorably situated for excision with minimal risk of producing a major functional deficit, (2) small malformation associated with prior minor bleeding and situated in an important functional region and (3) some malformations previously considered inoperable because of depth or size or both. These inclusions evolved as a direct consequence of three factors: (1) improved angiographic delineation of afferent and efferent ves-

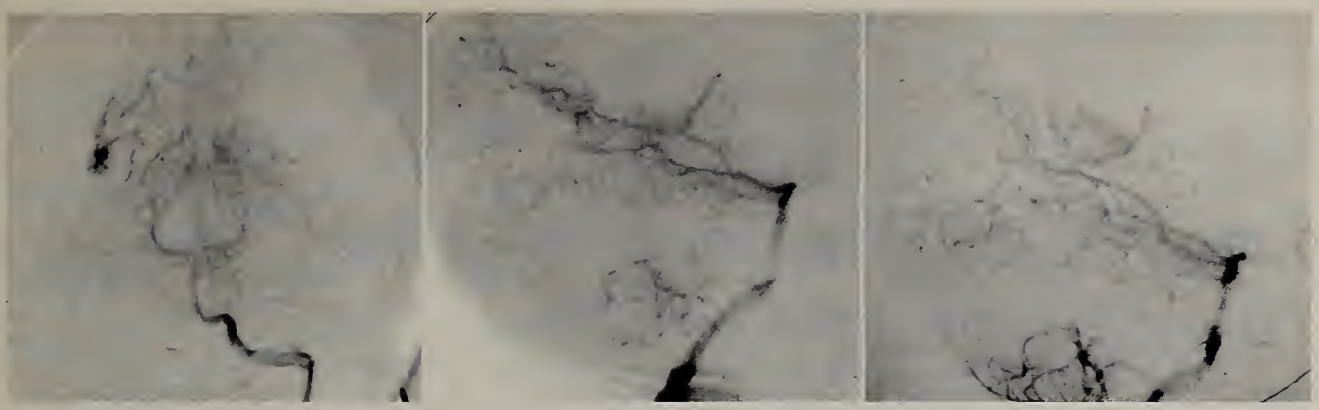


Figure 5.—(Case 12) **Left,** preoperative arteriovenous malformation (AVM) in the right occipital lobe (anteroposterior view). **Center,** preoperative AVM in the right occipital lobe (lateral view). **Right,** postoperative (first operation) showing the residual anteriorly placed segment of the AVM.

sels, (2) bipolar coagulation and (3) the operating microscope. Others, particularly Kunc,[19] have reached similar conclusions.

Improved illumination and magnification afforded by the operating microscope allow more precise excision and protection of adjacent normal brain. Intraoperative angiography and repeated injections of cardiac green for direct visual verification of critical afferent and efferent vessels have been used selectively. These techniques are especially helpful in accurately localizing small deep malformations, and for extensive malformations where the meshwork of vessels can be confusing.

The surgical mortality rate and postoperative follow-up status in the present series compare favorably with other series as reported by Kunc,[19] Morello,[10] Paterson and McKissock,[12] Forster[9] and Moody.[8] Patients presenting with hemorrhage have been free of recurrence after total excision or obliteration. Contrary to the experience of others,[1,2,8-10] we excised six lesions in patients who presented with seizures and, in follow-up, seizures have not recurred. However, the period of observation is short, and anticonvulsant medication has been continued in all cases. One patient who presented with intracerebral hemorrhage developed grand mal seizures that are now controlled by medical management.

Postoperative angiographic study is important, particularly in cases where total excision of the lesion is in doubt. In all patients, postoperative angiograms have confirmed total excision. One patient (illustrated in Figure 5) was shown to have residual malformation and a second procedure was carried out with angiographically-confirmed total removal. Smacher and coworkers[16] reported their unfavorable experience with incompletely removed malformations underlining the indication for postoperative angiography.

REFERENCES

1. Cushing H, Bailey P: Tumors Arising From the Blood Vessels of the Brain. Springfield, Ill., Charles C Thomas, 1928
2. Dandy WE: Arteriovenous aneurysm of the brain. Arch Surg 17:190, 1928
3. Dandy WE: The Brain—A Classical Reprint. New York, Hoeber Medical Division, Harper and Row, 1969
4. Kaplan HA, Aronson SM, Browder EJ, et al: Vascular malformation of the brain—An anatomical study. J Neurosurg 18: 630-635, 1961
5. Hamby WB: The pathology of supratentorial angioma. J Neurosurg 15:65-75, 1958
6. McCormick WF: The pathology of vascular ("arteriovenous") malformation. J Neurosurg 24:807-816, 1966
7. Olivecrona H, Riives J: Arteriovenous malformation of the brain. Arch Neurol Psychiatry 59:567-602, 1948
8. Moody RA, Poppen JL: Arteriovenous malformation. J Neurosurg 32:503-511, 1970
9. Forster DMC, Steiner L, Hakanson S, et al: Arteriovenous malformation of the brain. J Neurosurg 37:562-570, 1972
10. Morello G, Borghi GP: Cerebral angiomas. Acta Neurochir 28:135-155, 1973
11. Potter JM: Angiomatous malformation of the brain. Ann Royal College of Surg 16:227-243, 1955
12. Paterson JH, McKissock W: A clinical survey of intracranial angiomas with special reference to their mode of progression and surgical treatment. Brain 79:233-265, 1956
13. Henderson WR, Gomez R: Natural history of cerebral angiomas. Br Med J 4:571-574, 1967
14. MacKenzie I: The clinical presentation of cerebral angioma. Brain 76:184-214, 1953
15. Waltimo O: The relationship of size, density, and localization of intracranial arteriovenous malformation to the type of initial symptom. J Neurol Sci 19:13-19, 1973
16. Smacher AL, Allcock JM, Drake CG: Cerebral angiomas: The sequelae of surgical treatment. J Neurosurg 37:571-575, 1972
17. Perret G, Nishioka H: Arteriovenous malformation—An analysis of 545 cases of craniocerebral arteriovenous malformation and fistulas reported to the cooperative study. J Neurosurg 25:467-490, 1966
18. Waltimo O: The change in size of intracranial arteriovenous malformation. J Neurol Sci 19:21-27, 1973
19. Kunc Z: Surgery of arteriovenous malformation in the speech and motor-sensory regions. J Neurosurg 40:293-303, 1974
20. Norlen G: Arteriovenous aneurysms of the brain. J Neurosurg 6:475-494, 1949
21. Pool JL: Treatment of arteriovenous malformation of the cerebral hemisphere. J Neurosurg 19:136-141, 1962

Refer to: Oberman AE, Chatterjee SN: Ocular complications in renal transplant recipients. West J Med 123:184-187, Sep 1975

Ocular Complications in Renal Transplant Recipients

ARTHUR E. OBERMAN, MD, *and* SATYA N. CHATTERJEE, FRCS (Eng, Edin, Glasg)
Los Angeles

Twenty-five patients were examined for ocular complaints following renal transplantation. Besides the expected complications of posterior subcapsular cataract and cytomegalovirus retinitis, other findings—such as focal depigmentation of the retinal pigment epithelium, a lack of hypertensive retinopathy, elevated intraocular tensions, microaneurysms, preretinal wrinkling, serous detachments of the retina, hemorrhages and exudates—were observed.

A laboratory clue to the onset of cytomegalovirus retinitis was a rapid rise in cytomegalovirus (CMV) antibody titer and a positive CMV plaque count in tissue culture.

Most of the ocular complications following renal transplantation are recognized as secondary to immunosuppressive drugs, especially to the use of corticosteroids.[1] This report is an examination of the ocular complications in a series of patients who had received renal transplants, emphasizing the multiplicity of findings and the importance of laboratory aids to early diagnosis.

Of 143 patients who received renal transplants at the Los Angeles County-University of Southern California Medical Center between March 1968 and April 1974, 25 were selected because of visual complaints. Their ages ranged from 22 to 52 years. Transplantation had been done in all of them between 5 to 61 months before eye examination. Before operation, all patients had received maintenance hemodialysis. Following transplantation, routine immunosuppression with azathioprine (Imuran®) and prednisone was administered as described by Silcott and associates.[2] Antirejection therapy, when necessary, consisted of three doses of intravenously given methylprednisolone (Solu-Medrol®) administered on alternate days at a dose of 20 mg per kg body weight. Eleven of the 25 patients received, in addition, local irradiation of 200 rads to the graft on alternate days for three doses (Table 1).

Transplants were done for varied reasons (Table 2), none of which was considered more pertinent than another with respect to ocular complications found in this series. Diabetes, presumed to be steroid induced, developed in the post-transplant period in five patients of the

From the Departments of Ophthalmology (Dr. Oberman) and Surgery (Dr. Chatterjee), Los Angeles County-University of Southern California Medical Center, Los Angeles.

Submitted April 28, 1975.

Reprint requests to: A. E. Oberman, MD, LAC-USC Medical Center, P.O. Box 568, 1200 North State Street, Los Angeles, CA 90033.

TABLE 1.—*Summary of Patients and Findings*

Patient Number, Age in Years and Sex	*Diabetes*	*Hypertension*	*Deep X-ray to Graft*	*Cytomegalovirus Status (U=Viruria, B=Viremia)*	*Total Prednisone Dose, Grams*	*Eye Findings*	*Months from Transplant*
1. 38 ♂	No	No	Yes	Neg.	256	Cataract retinal cyst	36
2. 35 ♀	No	No	No	Neg.	..	..	5
3. 33 ♂	No	No	Yes	+ U	..	..	15
4. 49 ♂	Yes	Yes	No	+ B U	..	Inc. IOP	17
5. 48 ♀	No	No	Yes	Neg.	..	Cataract	7
6. 34 ♂	No	Yes	Yes	Neg.	..	Glaucoma	13
7. 41 ♂	No	No	No	Neg.	..	Inc. IOP, depigmentation	29
8. 31 ♂	No	Yes	Yes	Neg.	297	Cataract, depigmentation	41
9. 25 ♂	Yes	No	No	+ B U	275	Cataract	25
10. 52 ♂	No	Yes	Yes	Neg.	..	Cataract, depigmentation	44
11. 49 ♀	No	No	No	Neg.	..	..	61
12. 35 ♂	No	Yes	No	+ U	334	Cataract	20
13. 45 ♀	Yes	Yes	Yes	+ B U	345	Cataract	21
14. 43 ♂	Yes	No	No	Neg.	330	Cataract	32
15. 49 ♂	No	Yes	Yes	Neg.	..	Preretinal membrane	40
16. 22 ♀	No	Yes	No	+ B U	179	Cataract, CMV retinitis	13
17. 36 ♂	No	Yes	No	+ U	..	Rubeosis iridis	54
18. 30 ♂	No	Yes	No	+ B U	225	Cataract, Inc. IOP	18
19. 27 ♀	No	Yes	No	+ B U	..	Cataract	16
20. 23 ♀	No	Yes	Yes	+ B U	..	..	16
21. 30 ♂	No	Yes	No	+ U	..	Depigmentation	8
22. 25 ♂	No	No	No	+ B U	206	Cataract, depigmentation	37
23. 37 ♂	Yes	Yes	Yes	+ B U	221	Cataract	13
24. 24 ♀	No	Yes	Yes	+ B U	217	Cataract, CMV retinitis	37
25. 37 ♂	No	Yes	No	+ B U	261	Cataract, Inc. IOP	17

Inc. IOP = Increased intraocular pressure
CMV = Cytomegalovirus

TABLE 2.—*Causes of Primary Renal Failure*

Disorder	*Number*
Glomerulonephritis	13
Pyelonephritis	3
Nephrosclerosis	4
Polycystic kidney	2
Hypoplasia of the kidney	2
Disseminated lupus erythematosus	1

group. Blood glucose was maintained at a level of 200 to 300 mg per 100 ml by dietary and drug therapy. Sixteen of the patients had persistent diastolic blood pressures greater than 100 mm of mercury, despite treatment with antihypertensive drugs.

The eye examination consisted of measurement of visual acuity with and without correction, slit lamp examination, applanation tonometry, indirect ophthalmoscopy and color fundus photography.

Viral cultures in human fibroblast cultures were obtained from blood (buffy coat) and urine, as described by Fiala and associates.[3] Isolation of cytomegalovirus required 10 to 30 days from urine specimens and 20 to 40 days from buffy coat cells separated from heparinized peripheral blood. Complement fixation (CF) studies with cytomegalovirus (Strain AD-169) antigen were performed by the microtiter modification of the Kolmer technique (California State Health Department). The highest dilution of serum resulting in 3+ or 4+ fixation was considered as the CF titer.

Results

Ocular complications were found in 21 of the 25 patients. In some cases, more than one complication was present. In 15 patients the presence of cataract was noted; all cataracts being bilateral and posterior subcapsular in type. The opacity varied in appearance, from wispy cortical strands causing no visual impairment to dense white posterior plaques causing significant visual loss. The total dose of prednisone given after transplantation to the patients with cataract varied from 179 to 484 grams (Table 1).

The next most frequent ocular complication was bilateral depigmentation of the retinal pigment epithelium, noted in five patients. Many variations in extent and degree of depigmentation were noted; however, no case was accompanied by pigment clumping. The depigmentation

Figure 1.—Fundus photograph of multiple irregular areas of depigmentation of the retinal pigment epithelium in a renal transplant recipient.

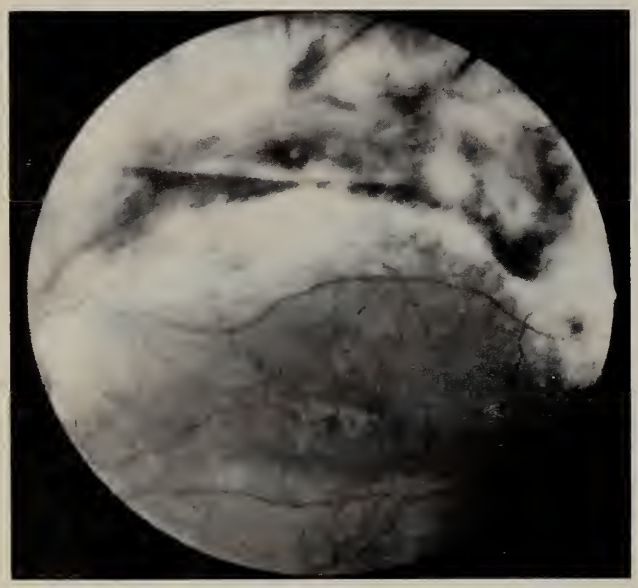


Figure 2.—Acute retinitis due to cytomegalovirus. Hemorrhagic vasculitis of the superior temporal retinal vessels surrounded by massive white banks of retinal necrosis.

was frequently in the perimacular area, and occasionally seen in multiple areas of the midperiphery of the fundus (Figure 1).

Elevated intraocular tension, as measured by tonometry, was found in five patients of the series. Glaucomatous cupping of the optic disc was noted, however, in only one of these.

The major disabling ocular complication was bilateral cytomegalovirus (CMV) retinitis, discovered in two patients (Figure 2). In one, loss of vision in one eye prompted examination of the patient; in the other, it was a chance discovery on routine indirect ophthalmoscopy. The syndrome was identified by the distinctive pattern of widespread retinal necrosis and vasculitis.[4]

Despite the fact that 16 of the 25 patients were hypertensive (sustained diastolic blood pressure greater than 100 mm of mercury), retinal vascular changes of hypertension were infrequently seen. In only two patients was there segmental arteriolar narrowing, and in seven patients there were scattered superficial retinal hemorrhages.

Less frequent complications noted were microaneurysms, deep retinal hemorrhages, hard exudates, soft exudates, preretinal wrinkling and serous detachment of the retina.

Discussion

The true frequency of ocular complications, after renal transplantation and the necessary immunosuppressive therapy, cannot be determined by this study, since only patients with complaint of ocular symptoms were examined. Previous reports have defined the major complications of cataract and cytomegalovirus retinitis.[4-8] The development of posterior subcapsular cataract has been firmly related to the extended use of systemic steroids.[1,9] The total dose that is critical to cataract formation is considered in conflicting reports.[1,8] In this study, the density of cataract and consequent visual loss could not be related to total corticosteroid dose, the duration of survival from the time of transplant or the age of the patient.

Cytomegalovirus retinitis is an example of a retinal response to an organism of low virulence in an immunologically compromised host. The ineffectiveness of reducing systemic steroids to halt the fulminating course of the disease confirmed other reports.[4,5] Detection of retinitis is aided by careful monitoring of buffy coat culture plaque count and recognition of a rising complement fixation titer of antibody.

Findings, other than cataract and retinitis, have not been previously considered characteristic of this patient population. The lack of hypertensive retinopathy in a patient group, the majority of which were hypertensive, is most unusual.[7]

Focal depigmentation, if related to transplantation and antirejection therapy, is a new finding. Since these patients were relatively young, senile degeneration could not be considered an etiologic factor. One possibility would be an unidentified

virus in the immunosuppressed tissue. The fact that cytomegalovirus inclusions have been found in pigment epithelium of renal transplant recipients[4,6] should raise the possibility that other viruses also could be present. In an unrelated ocular disorder called acute posterior multifocal placoid pigment epitheliopathy,[10] a characteristic alteration of the pigment epithelium is considered to be of possible viral cause. Another mechanism for depigmentation may be hypertensive changes in the choroid. Lack of sufficient hypertensive retinal findings makes this unlikely.

REFERENCES

1. Porter R, Crombie AL, Gardner PS, et al: Incidence of ocular complications in patients undergoing renal transplantation. Br Med J 3:133-136, Jul 15, 1972

2. Silcott GR, Barbour BH, Mendez R, et al: Functional recovery from acute rejection as a guide to ultimate renal graft survival. Arch Surg 104:791-793, Jun 1972

3. Fiala M, Edmondson L, Guze LB: Simplified method for isolation of cytomegalovirus and demonstration of frequent viremia in renal transplant patients. Proc Soc Exp Biol Med 144:872-876, Dec 1973

4. DeVenecia G, Zu Rhein GM, Pratt MV, et al: Cytomegalic inclusion retinitis in an adult—A clinical, histopathologic, and ultrastructural study. Arch Ophthalmol 86:44-55, Jul 1971

5. Aaberg TM, Cesarz TJ, Rytel MW: Correlation of virology and clinical course of cytomegalovirus retinitis. Am J Ophthalmol 74:407-417, Sep 1972

6. Wyhinny GJ, Apple DJ, Guastella FR, et al: Adult cytomegalic inclusion retinitis. Am J Ophthalmol 76:773-781, Nov 1973

7. Berkowitz JS, David DS, Sakai S, et al: Ocular complications in recent transplant recipients. Am J Med 55:492-495, Oct 1973

8. Hovland KR, Ellis PP: Ocular changes in renal transplant patients. Am J Ophthalmol 63:283, 1967

9. Black RL, Oglesby RB, Von Sallman L, et al: Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. JAMA 174:166, 1960

10. Ryan SJ, Maumanee AE: Acute posterior multifocal placoid pigment epitheliopathy. Am J Ophthalmol 74:1066-1074, Dec 1972

Cocaine: Its Use in Otolaryngology

Cocaine is the only local anesthetic with inherent vasoconstrictive abilities, a sine qua non for effective intranasal surgery. Other applications include shrinkage of mucous membranes, vasoconstriction and anesthesia. If we grant then the myriad usage of cocaine in ear, nose and throat practice, why the objection to its use? The answer lies in its toxicity.

In spite of the warning issued 50 years ago against the usage of cocaine mud (a mixture of cocaine flakes and 1:1,000 epinephrine), it is still widely accepted. The effectiveness of vasoconstrictors in retarding absorption of injected local anesthetics is proven, but the addition of epinephrine in topical application may actually be harmful. Vasoconstrictors do not retard absorption from the mucous membrane and while they may intensify the shrinkage of the mucous membrane, deleterious effects of the epinephrine itself should preclude its use in combination with cocaine. In addition, cocaine sensitizes the patient to exogenous epinephrine.

Is there an acceptable alternative? A totally suitable synthetic topical anesthetic has not been forthcoming. No one compound, nor even a combination of substances, has been able to provide the mucous membrane anesthesia, tissue shrinkage, vasoconstriction, duration of action and acceptable level of toxicity possessed by the extract of Erythroxylon coca. We are led then to the inevitable conclusion that cocaine remains a vital instrument in the otolaryngologist's armamentarium, and can make the following recommendations: Cocaine in the hands of knowledgeable and cautious physicians is an unexcelled topical anesthetic and is certainly not habit forming to the patient.

—NICHOLAS L. SCHENCK, MD, *El Paso*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 7, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Blumberg BD, Golbus MS: Psychological sequelae of elective abortion. West J Med 123:188-193, Sep 1975

Psychological Sequelae of Elective Abortion

BRUCE D. BLUMBERG, MD, *and* MITCHELL S. GOLBUS, MD, *San Francisco*

A mild, short, depressive and guilt ridden period following abortion is quite common, but a severe psychological reaction is rare. The indication for the abortion and the preabortal psychological state of the patient are the two most important factors. Almost all reported instances of postabortion psychoses have occurred in patients who had severe preabortal psychiatric problems. Women undergoing abortion for socioeconomic or psychosocial indications appear to be at minimal risk for long-term negative psychological sequelae. In contrast, women in whom abortion is carried out because of exposure to rubella and the risk of fetal malformation, maternal organic disease or the prenatal diagnosis of a genetically defective fetus are at greater risk and may need supportive psychotherapy.

THE LITERATURE concerning the psychiatric consequences of abortion is as confusing as it is profuse. In the past 40 years, opinions have been presented from every perspective. Much of the information is devalued by the overt interjection of personal opinions and prejudices concerning the morality of abortion. Even after it was realized that scientific studies were necessary to elucidate the psychological components of abortions, many inquiries were handicapped by the use of inadequate methods for the study of the very complex and subjective phenomena involved. A number of noteworthy reviews are scattered throughout the psychiatric literature, but the subject has received little attention in the obstetric literature.[1-5]

We will attempt to clarify this confusion by artificially grouping the material according to the basic orientation of the author. The first references will be those classified as *impressionistic,* a term used to describe material presenting an opinion based upon clinical experience. The label *psychoanalytic* will be applied to the studies which invoke theoretical psychiatric concepts of pregnancy and its termination. The *data analysis* studies present data derived from the application of a specific methodology. These categories are intended to simplify the presentation of a heterogeneous mass of information, and many references fit into more than one category. No value judg-

From the Departments of Obstetrics and Gynecology and of Pediatrics, University of California School of Medicine, San Francisco.

Submitted February 18, 1975.

Reprint requests to: M. S. Golbus, MD, Department of Obstetrics and Gynecology, University of California Medical Center, San Francisco, CA 94143.

ment is intended; an impressionistic study based upon years of astute clinical observation may be more noteworthy than a data analysis study in which an ill-conceived methodology is used.

Impressionistic Studies

Many of the earliest papers on the subject dealt with the emotional consequences of illegally induced abortions, since legally induced abortions were rare until recent years. Taussig[6] warned of the possible outcome of abortion: "not only is the immediate psychic state to be dreaded, but . . . many a mental case, after careful analysis will be shown to date back to the terrifying experience of an induced abortion." He cited several case reports suggesting that sexual anesthesia, dyspareunia, marital quarrels, frigidity, psychoneurosis, depression, irritability or divorce could occur in the wake of abortion, and he concluded that the immediate danger was very serious and the remote harmful sequelae manifold.[7]

Contrary opinions were reported during the 1950's. Mandy,[8] in his "Reflections of a Gynecologist," argued against the exaggerated and frightening warnings of the frequency with which serious depressions may follow induced abortions. His view was supported at the same conference by Lidz,[9] who argued that many women have abortions with relief and with little, if any, subsequent disturbance. Lidz observed very few serious psychiatric reactions following an induced abortion and felt they were rarer than the severe emotional reactions to unwanted pregnancy, childbirth and the responsibilities of motherhood. Kraepelin[10] had argued that abortion more often alleviates than precipitates mental disease, and Pearce[11] noted that this concept had evolved to the tacit assumption that abortion per se had a therapeutic effect and few, if any, bad effects. He indicated that this newer concept required substantiating studies.

The divergence of opinion regarding the potential deleterious psychological effects of abortion has continued during this past decade. MacDonald[12] asserted that following abortion the initial feelings of anxiety and depression fade in time but are replaced by a lasting sense of guilt. Gluckman[13] reported several cases and concluded that abortion may lead to unforeseen psychoses, neuroses and psychosomatic disorders, with special emphasis on gynecologic symptomatology. He felt such sequelae were more likely to be encountered in an emotionally unstable and psychiatrically predisposed patient. Following the liberalization of the abortion law in Colorado, a preliminary survey of 168 abortion patients showed no untoward emotional reactions in the immediate or delayed postoperative periods.[14]

There have been two opinion surveys of psychiatrists published. Kummer[15] found that 75 percent of 32 California psychiatrists had not encountered any moderate or severe psychiatric sequelae of abortion; the others encountered such sequelae only rarely, the highest figure being six cases in 15 years of practice. Kummer also noted that the Mothers Aid Society of Copenhagen reported no psychiatric aftereffects of moderate or severe degree among approximately 30,000 legal abortion patients. The second survey reported a number of psychiatrists who felt that even if there were no immediate psychological traumata from abortions, psychological scars caused by guilt, regret and depression would be seen later in life. The authors, however, questioned why so few of the estimated million abortions per year result in psychiatrically traumatized women coming to the attention of society.[16]

Psychoanalytic Studies

Deutsch[17] observed that accidental pregnancy unleashed the conflict between the instinct of self-preservation and the urge for motherhood. A possible solution to this dilemma is abortion. This course of action may produce depression in a woman who has a compulsion to conceive, elation in a woman who views pregnancy as an external compulsion, or self-accusation in a woman prone to excessive guilt reactions. Deutsch suggested that even in an unwanted pregnancy, maternal identification with the fetus is characteristic and abortion is likely to arouse feelings of self-destruction. This sense of personal self-sacrifice may irreparably damage the previously stable heterosexual relationship which produced the pregnancy in question. De Beauvoir[18] emphasized the ambivalence engendered by abortion which can lead to self-deprecation. Even when a woman consents to abortion, she feels it is a sacrifice of her femininity and sees her sex as a kind of infirmity and a curse. Dunbar[19] supported this concept of ambivalence, arguing that a woman would experience both relief and deprivation after an abortion but would begin to blame her husband or society for her dilemma and possibly lose conviction in playing the feminine role.

In a study of 150 abortion patients, Senay[20] claimed that more than 90 percent underwent a mourning process which was completed preconsciously or unconsciously, with a rapid resolution of crisis symptoms representing a maturational step. When pregnancy, a potential child or a stay in hospital are focussed upon, awareness of guilt, depression or anxiety could persist for several months after an abortion. Complete resolution or repression usually required a number of months after an abortion. Fleck[21] suggested that unfavorable abortion sequelae are magnified in the literature by the presentation of single case reports, and he emphasized that every surgical operation, every inroad on a person's body, leaves psychological scars. He stressed that the psychopathogenic conditions of a hospital stay and disapproving societal attitudes enhance the development of conflict, guilt and shame in a woman in whom abortion has been carried out. Raphael[22] added that a woman whose religious beliefs, moral convictions or cultural background conflict with her desire or need for abortion may be at a much higher risk of a postabortal psychological complication, particularly in the form of excessive guilt. She noted that the husband or putative father may also require reassurance and the opportunity to talk over his own feelings of loss, guilt and anger.

Data Analysis Studies

The desire to make data analysis studies arose from the recognition that impressionistic studies might be biased by recall of particularly outstanding cases in an author's own experience, and by remembering what confirmed a writer's own beliefs. Psychoanalytic studies also may be influenced by the prejudices of an investigator, as shown by Bolter[23] who proclaimed "woman's main role here on earth is to conceive, deliver and raise children. Despite all other sublimated types of activity, this is still their primary role. When this function is interfered with, we see all sorts of emotional disorders . . . " It is not difficult to imagine the conclusions of his studies.

However, the data analysis protocols have their own problems. Many attempt to follow up abortion patients by mailed questionnaire; the respondents, a self-selected subgroup, may not represent the total population. If personal interview is used, then care must be taken to avoid the interjection of observer bias in collecting the data, and standardization of a pool of such subjective data into a reportable form may also be difficult. The results of psychometric tests are useful only to the extent that they can be compared with a control group, and it is difficult to define the appropriate control group in this instance. Should it be the general population? Pregnant women? Women who desire but are refused abortion? It is important to keep these problems in mind as we review data analysis studies.

Hamilton[24] interviewed 537 women within 24 hours of abortion, but only 30 had received elective terminations and the remainder had spontaneous or illegal abortions. More than half of the patients in whom abortion had been electively induced expressed relief or satisfaction while 23 percent felt regret. Further interpretation is impossible because the investigator failed to distinguish between those who had elective and those who had spontaneous abortions. Malmfors[25] reported a 37 percent incidence of guilt feelings, and a 12 percent incidence of impaired mental health (anxiety, neurosis, depression or psychosis) in a series of 84 women who had had abortions; all with impaired mental health had exhibited various neurotic complaints before the procedure. Ekblad[26] detailed the sequelae of abortion in 479 women, 25 percent of whom admitted self-reproach and approximately half of this subgroup described serious self-reproach or regret. However, their depression was generally mild from a psychiatric viewpoint, with only 1 percent of the entire group reporting a reduction in work capacity—and in all of these there had been severe neurotic symptoms before abortion. When only women with normal personalities were considered, the incidence of serious self-reproach fell to 6 percent, with no resultant psychiatric illness. Ekblad also showed that psychiatric consequences were unrelated to age, intelligence, parity, marital status, subsequent pregnancy, concomitant sterilization or occupation. However, in those women who obtained abortion after coercion by spouse or family, there was a higher incidence of undesirable sequelae (the only factor other than premorbid personality to show such an influence). Mehlan[27] reported that 90 percent of 243 German women who had abortions six years earlier still felt that elective abortion had been the proper course of action, while 10 percent regretted the procedure. In a similar Danish study of 135 patients, 83 percent were "glad without reserve," 10 percent "satisfied but doubtful," 4 percent "not happy

but know the abortion was necessary" and 4 percent "repentant."[28]

Arén[29] studied 100 women who became pregnant and gave birth after an earlier elective abortion; 14 stated they had conceived to have a substitute for the aborted "child," and 20 claimed they could not tolerate another abortion even though this pregnancy was unwelcome. Arén concluded that these 34 women provide evidence that their guilt feelings cannot be regarded as trivial, but rather as a serious complication following elective abortion. Gebhard and co-workers[30] interviewed a large group of women who had an illegal abortion. They found that less than 10 percent experienced psychological upset following the procedure and concluded that although there appeared to be little psychological trauma in most cases, a considerable amount of unfavorable reaction may show up in a few, and that the ill effects after induced abortion appeared less frequently than previously assumed. Hong[31] reported that 90 percent of a large group of Korean women described little or no guilt feelings after resorting to abortion. In contrast to findings in the Scandinavian studies, he found that young wives, wives with fewer pregnancies and wives with higher educational background and greater knowledge of contraceptive methods had greater guilt feelings toward the induced abortion.

Osofsky and co-workers,[32] who interviewed 250 women shortly after their abortion, reported that 15 percent displayed mild depression. Of the total, 76.2 percent denied guilt feelings while 15.6 percent described some guilt and 8.2 percent described considerable guilt. Some self-reproach was claimed by 7.2 percent, and 1.5 percent were very angry with themselves and negative about their decision to have the abortion. When Opton[33] looked at the same question somewhat later after the procedure, only 6 percent of his group had any regrets about having had the abortion. The women generally described a very short period of depression followed by a prompt return to their prepregnant mental state. The Hungarian experience has been that the women most likely to suffer emotional upset after abortion are those who have shown ambivalence in relation to the pregnancy before the abortion.[34]

Another group of patients who seem to be at more risk for detrimental psychological sequelae of abortion are adolescents. Wallerstein and co-workers[35] found that at five to seven months postabortion, only 50 percent of teenagers had mastered the pregnancy and abortion experience to the point of returning to their previous state of psychosocial functioning.

Several studies in the past decade have used psychometric testing to clarify the nature of emotional responses to abortion. In a prospective psychometric study, Brody and associates[36] found abnormal psychiatric profiles of abortion applicants, with improvements at six weeks postabortion, and further return to normal at one year after the procedure. Margolis and co-workers[37] found that approximately half the women seeking abortion showed psychometric elevation on scales depicting depression, psychopathic deviation or schizophrenia; and more than half of these had normal psychometric profiles after the abortion. In a similar study, Niswander and co-workers[36] administered psychometric tests to 58 women undergoing abortion and found the postoperative test scores at six months postabortion were significantly lower than the preoperative scores for maladjustment, depression and anxiety. While there was a significant reduction in stress, the scores still indicated that these patients were more depressed and less well adjusted than a control group of maternity and gynecologic patients.

Indication for Abortion

A number of investigators have questioned whether the psychological sequelae of elective abortion might vary with the indication for the procedure. Jansson[39] noted that only 0.2 percent of patients undergoing spontaneous or illegal abortion for socioeconomic reasons were admitted to the hospital for psychiatric treatment after the procedure, whereas 1.92 percent of 1,773 Swedish women who had legal abortions because of increased "psychic vulnerability" required admission to hospital for psychiatric reasons after the procedure.

Peck and Marcus[40] compared two groups of 25 women who had had abortions for either psychosocial reasons or because of an exposure to rubella with an increased risk of fetal malformation. The most striking difference between these two groups was their conscious wish for the current pregnancy—96 percent in the psychosocial group did not want the pregnancy, contrasted with 40 percent of the rubella group who did not. A mild and brief depression was reported by only one woman in the psychosocial group but by nine women in the rubella group. All had recovered within three

to six months after the abortion, without psychiatric treatment. Of the 50 women, 49 would have chosen to repeat the abortion if the situation recurred, although 6 expressed some regrets about having had the abortion. The groups also differed in that the rubella group more commonly conceived or desired a subsequent pregnancy soon after the abortion.

Niswander and Patterson[41] reported similar data. Of 90 patients given abortions for psychosocial indications, 23.3 percent noted a negative immediate effect and 12.2 a negative long-term effect. Of 17 patients aborted because of exposure to rubella, 64.7 percent noted negative immediate effects and 47.1 percent negative long-term effects. Of nine patients aborted because of maternal organic disease, 55.6 percent noted a negative immediate effect but only 11.1 percent a negative long-term effect. McCoy[42] also found that the incidence of short-term regrets was twice as great in women aborted for medical indications when compared with women aborted for psychosocial indications, but that the long-term regrets occurred with similar frequency in both groups. Pare and Raven[43] showed that mild feelings of guilt or loss were not unusual after abortion for psychosocial indications, usually lasting only one to two weeks—and in only 13 percent existing longer than three months. In contrast, 6 of 14 women in whom an organic disease was the primary indication for abortion were very upset and developed severe symptoms of depression.

Simon and associates,[44] who used psychometric testing to clarify the nature of emotional responses to abortion, found that 67 percent of 16 women given abortions for psychosocial reasons reported positive responses and feelings of relief, 25 percent reported mild depression of one to two weeks duration and 9 percent reported pronounced depression. The corresponding figures for a group of 17 women aborted after exposure to rubella are relief in 38 percent, mild depression in 50 percent and pronounced depression in 12 percent. Of 12 women having abortions for medical indications, 50 percent felt relief, 25 percent felt mild depression and 25 percent felt pronounced depression. Consequently, it seems that a depressive reaction to the abortion experience was more characteristic of those patients having abortions for fetal or medical indications. Guilt feelings were noted much more frequently in those women who were sterilized following the abortion.

Abortion Carried Out for a Genetic Indication

Follow-up studies of women who had an amniocentesis specifically for the prenatal detection of a genetic defect in the fetus have noted that feelings of guilt, doubt and ambivalence were common.[45,46] The risk of psychosocial trauma to a family which elects therapeutic abortion upon being told the fetus is genetically defective was recently evaluated by studying 13 families in which the woman had undergone amniocentesis and selective abortion.[47] Only 2 of 13 women and 4 of 11 men in that study failed to mention depression in describing their emotional reaction to abortion. Of the 6 nondepressed persons, 1 woman and 2 men had Minnesota Multiphasic Personality Inventory (MMPI) profiles reflecting a tendency to deny emotional problems, so that the actual incidence of depression following selective abortion may have been as high as 12 of 13 (92 percent) among the women and as high as 9 of 11 (82 percent) among the men studied. The role of decision making and the responsibility associated with selective abortion may explain the more serious depression observed in these patients, compared with that following an elective abortion for psychosocial indications.

Even when selective abortion is accepted as the preferable alternative to the birth of a defective child, the responsibility for making the decision to abort may prove to be an uncomfortable burden for the parents. There is also the additional problem of the sense of guilt and shame associated with genetic disease. Fletcher[45] noted that "added to the guilt associated with being a carrier of genetic disease was the realization that their experiment to get a healthy child had failed." An amniocentesis result indicating a genetically defective fetus may reignite the depression, guilt, or frustration associated with the birth of a previously affected child or close relative.

Selective abortion is by technical necessity a second trimester procedure. It has been suggested that late abortion conveys a greater emotional impact than does earlier abortion.[48] Bibring and co-workers[49] argued that quickening is the physiological event which signals maturation from the narcissism and self-cathexis of early pregnancy to a view of the fetus as an object of increasingly independent existence. After quickening, the fetus comes to be considered a potential future child and there is proliferation of fantasies concerning the child's sex, appearance or talents.[50]

Summary

The incidence of deleterious psychological sequelae to elective abortion should be assessed in comparison with the incidence of postpartum deleterious emotional reactions. While postpartum psychosis occurs in only 0.1 to 0.2 percent of pregnancies, simpler depressive reactions are far more common. Impressionistic, psychoanalytic and data analysis studies suggest that a severe psychiatric reaction after abortion is rare but that a mild, short, depressive and guilt-ridden period following an abortion is quite common. The indication for the abortion and the preabortal psychological state of the patient are the two most important factors. Almost all postabortal psychoses occur in patients who had severe preabortal psychiatric problems. Women having abortion for socioeconomic or psychosocial indications appear to be at minimal risk for long-term negative psychological sequelae and see the abortion as a solution to an undesired pregnancy and prevention of the birth of a "mistake." Women who have abortions because of exposure to rubella and the risk of fetal malformation, because of maternal organic disease or because of a prenatal diagnosis of a genetically defective fetus are terminating a desired pregnancy—and their action precludes the birth of a wanted child. In the latter group, more than a casual follow-up should be made, and they should be encouraged to seek psychiatric aid if their depressive or guilt feelings are severe or long-lived.

REFERENCES

1. Simon N, Senturia A: Psychiatric sequelae of abortion. Arch Gen Psychiat 15:378-389, 1966
2. White R: Induced abortions—A survey of their psychiatric implications, complications, and indications. Texas Rep Biol Med 24:531-558, 1966
3. Schwartz R: Psychiatry and the abortion laws—An overview. Compr Psychiat 9:99-117, 1968
4. Callahan D: Abortion: Law, Choice and Morality. New York, The MacMillan Company, 1970
5. Simon N: Psychological and emotional indications for therapeutic abortion, *In* Sloane R (Ed): Abortion: Changing Views and Practice. New York, Grune and Stratton, 1970 (also published in Seminars Psychiat 2(3):283-301, 1970)
6. Taussig F: Abortion, Spontaneous and Induced. St. Louis, CV Mosby Company, 1937, pp 276-278
7. Taussig F: Effects of abortion on the general heath and reproductive functions of the individual, chap 4, *In* Taylor H (Ed): The Abortion Problem—Proceedings of the conference held under the auspices of the National Committee on Maternal Health, Inc at the New York Academy of Medicine, June 19-20, 1942. Baltimore, Williams-Wilkins Co, 1944, pp 46-47
8. Mandy A: Reflections of a gynecologist, *In* Rosen H (Ed): Therapeutic Abortion. New York, Julian Press, 1954, pp 284-296
9. Lidz F: Reflections of a psychiatrist, *In* Rosen H (Ed): Therapeutic Abortion. New York, Julian Press, 1954, pp 276-284
10. Kraepelin E: Psychiatrie. Leipzeig, JA Barth, 1909
11. Pearce J: Discussion: The psychiatric indication for the termination of pregnancy. Proc Roy Soc Med 50:321, 1957
12. MacDonald R: Complications of abortion. Nurs Times 63(1):306-307, 1967
13. Gluckman L: Some unanticipated complications of therapeutic abortion. New Zeal Med J 74(471):71-78, 1971
14. Heller A, Whittington H: The Colorado story: Denver General Hospital experience with the change in the law on therapeutic abortion. Am J Psychiat 125(6):809-816, 1968
15. Kummer J: Post-abortion psychiatric illness—A myth? Am J Psychiat 119(10):980-983, 1963
16. Crowley R, Laidlaw R: Psychiatric opinion regarding abortion—Preliminary report of a survey. Am J Psychiat 124(4):559-562, 1967
17. Deutsch H: Psychology of Women. New York, Grune and Stratton, 1945
18. deBouvoir S: The Second Sex. Edited and translated by H Parshley. New York, Alfred A Knopf, Inc, 1952, pp 490-491
19. Dunbar F: A psychosomatic approach to abortion and the abortion habit, *In* Rosen H (Ed): Therapeutic Abortion. New York, Julian Press, 1954, pp 22-31
20. Senay E: Therapeutic abortion. Arch Gen Psychiat 23: 408-415, 1970
21. Fleck S: Some psychiatric aspects of abortion. J Nerv Ment Dis 151:42-50, 1970
22. Raphael B: Psychosocial aspects of induced abortion—Its implications for the woman, her family, and her doctor—Part 1. Med J Aust 2:35-40, 1972
23. Bolter S: The psychiatrist's role in therapeutic abortion—The unwitting accomplice. Am J Psychiat 119(4):312-316, 1962
24. Hamilton V: Some sociologic and psychologic observations on abortion. Am J Obstet Gynec 39:919-928, 1940
25. Malmfors K: Status of women after legal abortion. Svenska Larkartidingen 48:2445, 1951
26. Ekblad M: Induced abortion on psychiatric grounds—A followup study of 479 women. Acta Psychiat Neurol Scand Suppl 99:1-238, 1955
27. Mehlan KH: Spätfolgen nach Legalem Abort. Deutsche Gesundh 11:876-880, 1956
28. Kolstad P: Therapeutic abortions. Acta Obstet Gynec Scand 36:Suppl 6:7-72, 1957
29. Arén P: Acta Obstet Gynec Scand 37:Suppl 1, 1958, as cited by Year Book of Obstetrics and Gynecology, 1958-1959 Series. Edited by Greenhill. Chicago, Year Book Publishers. 1958, p 65
30. Gebhard P, Pomeroy W, Martin C, et al: Pregnancy, Birth, and Abortion. New York, Harper and Brothers and Paul B Hoebner, Inc, 1958, p 209
31. Hong S: Induced abortion in Seoul, Korea. IPPF: Proceedings of the Regional Conference, Western Pacific Region, 1965. Seoul, Dong—A Publishing Co, 1965, p 53
32. Osofsky J, Osofsky H, Rajan R, et al: Psychologic effects of legal abortion. Mod Treatm 8(1):139-158, 1971 (also published in Clin Obstet Gynec 14(1):215-234, 1971)
33. Opton E: Psychological and Social Outcomes of Abortion. Berkeley, California, The Wright Institute, 1971
34. Kapor-Stanulovic N: Three phases of the abortion process and its influence on women's mental health. Am J Public Health 62(7):906-908, 1972
35. Wallerstein J, Kurtz P, Bar-Din M: Psychosocial sequelae of therapeutic abortion in young unmarried women. Arch Gen Psychiat 27(6):828-832, 1972
36. Brody H, Meikle S, Gerritse R: Therapeutic abortion—A prospective study. Am J Obstet Gynec 109(3):347-353, 1971
37. Margolis A, Davidson L, Hanson K, et al: Therapeutic abortion follow-up study. Am J Obstet Gynec 110(2):243-249, 1971
38. Niswander K, Singer J, Singer M: Psychologic reaction to therapeutic abortion—Objective response. Am J Obstet Gynec 114(1):29-33, 1972
39. Jansson G: Mental disorders after abortion. Acta Psychiat Scand 41:87-110, 1965
40. Peck A, Marcus H: Psychiatric sequelae of therapeutic interruption of pregnancy. J Nerv Ment Dis 143(5):417-425, 1966
41. Niswander K, Patterson R: Psychologic reaction to therapeutic abortion—Subjective patient response. Obstet Gynec 29(5): 702-706, 1967
42. McCoy D: The emotional reaction of women to therapeutic abortion and sterilization. J Obstet Gynec Brit Cwlth 75:1054-1057, 1968
43. Pare C, Raven H: Follow-up of patients referred for termination of pregnancy. Lancet 1:635-638, 1970
44. Simon N, Senturia A, Rothman D: Psychiatric illness following therapeutic abortion. Am J Psychiat 124(1):59-65, 1967
45. Fletcher J: The brink—The parent-child bond in the genetic revolution. Theol Stud 33:457-470, 1972
46. Golbus M, Conte F, Schneider E, et al: Intrauterine diagnosis of genetic defects: results, problems, and follow-up of one hundred cases in a prenatal genetic detection center. Am J Obstet Gynec 118:897-905, 1974
47. Blumberg B, Golbus M, Hanson K: The psychological sequelae of abortion performed for a genetic indication. Am J Obstet Gynecol, In Press
48. Kaltreider N: Emotional patterns related to delay in the decision to seek legal abortion. Calif Med 118:23-27, May 1973
49. Bibring G: Dwyer T, Huntington D, et al: A study of the psychological processes in pregnancy and of the earliest mother-child relationship. Psychoanal Stud Child 16:9-72, 1961
50. Raphael B: Psychosocial aspects of induced abortion—Its implications for the woman, her family, and her doctor—Part 2. Med J Aust 2:98-101, 1972

Medical PROGRESS

Refer to: Gross SR: Animal models of glycogen storage conditions—Their relation to human disease (Medical Progress). West J Med 123:194-201, Sep 1975

Animal Models of Glycogen Storage Conditions

Their Relation to Human Disease

STEPHEN R. GROSS, PhD, *La Jolla, California*

THIS ARTICLE will briefly review the human glycogenoses and the mechanisms that regulate tissue glycogen concentrations. Biochemical studies of human glycogenoses will then be examined in light of recent studies on two animal models of glycogen storage conditions.

Human Glycogenoses

Although phosphorylase was originally proposed to be the enzyme responsible for both glycogen synthesis and degradation,[1] it is now clear that there are separate pathways for synthesis and degradation (Figure 1). Mutations in the enzymes of the synthetic pathway would not be likely to produce glycogen storage. One exception is the deficiency in the enzyme catalyzing the formation of the branch points in glycogen, commonly called brancher enzyme (Table 1). Persons with this mutation do not necessarily have an accumulation of glycogen in their tissues, but their glycogen has an abnormal structure.[8,9] The pathologic changes occurring in this syndrome are thought to result from the abnormal glycogen structure, but the exact mechanism is uncertain.[8,9] The remaining glycogenoses (Table 1) result from an altered regulation of glycogenolysis.

In the degradative pathway, two enzymes act directly on glycogen (Figure 1). Phosphorylase catalyzes the phosphorolytic cleavage of glycogen to glucose 1-phosphate, and debrancher enzyme hydrolyzes glycogen at branch points to glucose (Figure 1). Since glycogen is a highly branched polysaccharide and phosphorylase does not act on the branch points, the absence of either enzyme activity results in glycogen storage (Table 1).

Phosphorylase exists in two interconvertible forms, designated as *b* and *a*, that differ in their content of phosphate groups on specific serine residues.[10] The conversion of phosphorylase *b* to *a* is catalyzed by phosphorylase kinase (Figure 1) and the *a* to *b* conversion by phosphorylase phosphatase. Phosphorylase kinase also exists in a nonactivated, dephosphorylated form and an activated, phosphorylated form. The conversion of phosphorylase kinase to the activated form is catalyzed by adenosine-3′,5′-monophosphate (cyclic AMP)-dependent protein kinase, which also can phosphorylate glycogen synthase-I (independent of glucose 6-phosphate) to convert it to the nonactivated D form (dependent on glucose 6-phosphate for activity, Figure 1).[11] Deficiencies in the activity of phosphorylase kinase or cyclic AMP-dependent protein kinase have also been reported to produce glycogen storage disease in humans (Table 1).[12,13]

Two glycogenoses are associated with a deficiency in utilization of the products of glycogenolysis. One affects the liver whose glycogen content is an important source of blood glucose. The absence of hepatic glucose 6-phosphatase

From the Division of Pharmacology, Department of Medicine, University of California, San Diego, School of Medicine, La Jolla.

Supported in part by United States Public Health Service Grant GM 20412 and by a grant from the Muscular Dystrophy Associations of America.

Reprint requests to: S. R. Gross, PhD, 2026 BSB, Division of Pharmacology, Department of Medicine, University of California, San Diego, School of Medicine, La Jolla, CA 92037.

ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
AMP = adenosine monophosphate
Cyclic AMP = adenosine-3′,5′-monophosphate
G6-PD = glucose 6-phosphate dehydrogenase

activity blocks the conversion of glucose 6-phosphate to glucose, resulting in hypoglycemia and hepatic glycogen storage (Table 1). The products of glycogenolysis are also an ubiquitous source of substrate for the Embden-Meyerhof pathway and hence, for energy production. A deficiency of phosphofructokinase activity, a rate-limiting step in the Embden-Meyerhof pathway,[14,15] has been found to produce glycogen storage in skeletal muscle.[15] Tissue differences in the structure of phosphofructokinase may account for the limitation of this deficiency primarily to skeletal muscle.[15,16]

The remaining glycogenosis listed in Table 1 is associated with a decreased acid maltase activity.[17] In the classical presentation of this condition (Pompe's disease), death occurs in childhood.[9] Recently, less severe cases have been diagnosed in persons in the second to fifth decade of life.[18] The exact role of acid maltase in controlling tissue glycogen concentrations is not well understood (see Hers and van Hoof[17] for a further discussion).

Glycogenoses in Experimental Animals

There are only two glycogen storage conditions in experimental animals that have been extensively studied. These are deficiencies of liver glucose 6-phosphatase[19] and of skeletal muscle phosphorylase kinase,[20] both in the common house mouse, Mus musculus. The reasons for the lack of animal models of glycogenoses are undoubtedly multiple. A decreased glycogenolytic capability would be deleterious to survival in the wild, and lack of overt, pathognomonic features as seen, for example, in muscular dystrophies would mitigate against the ready recognition of such variants in animal colonies.

The glucose 6-phosphatase deficiencies were discovered among radiation-induced lethal mutations in X-irradiated mice.[19] Mice homozygous for the defective glucose 6-phosphatase die within several hours of birth from hypoglycemia.[19] Six different variants have been described that result in a glucose 6-phosphatase deficiency, and these variants are all alleles at the locus for albinism. In normal mice there is a pronounced rise in hepatic glucose 6-phosphatase within hours of birth; this rise fails to occur in the mutants.[19,21] Whether the glucose 6-phosphatase deficiencies in mice result from similar genetic changes as those reported in humans is uncertain.

The phosphorylase kinase deficiency mutation, on the other hand, is less deleterious. It is a single gene, sex-linked mutation (carried in I strain mice) associated with an elevation in skeletal muscle glycogen concentrations to three to five times that of control strains.[22] Affected animals have apparently normal muscle function.[20,22] This lack of a notably deleterious effect may be explained by the observation that fasting, exercise and even catecholamine administration stimulate glycogenolysis in skeletal muscle of I strain mice.[20,23] Early studies on this mutation found no significant phosphorylase kinase activity in I strain skeletal muscle extracts. Furthermore, no phosphorylase *b* to *a* conversion was observed in I strain skeletal muscle after epinephrine administration to the mice or electrical stimulation of isolated muscles to produce tetanic contractions, conditions that produce pronounced phosphorylase *b* to *a* conversion in skeletal muscle of control strains.[20,24] It was postulated that stimulation of phosphorylase *b* activity is the primary mechanism of action of glycogenolytic stimuli on I strain skeletal muscle.[22,24] Such a mechanism could be analogous to that postulated for hypoxic rat hearts in which a fall in tissue adenosine triphosphate (ATP) and glucose 6-phosphate concentrations and a rise in 5′-AMP and inorganic phosphate concentrations were observed with no increase in tissue phosphorylase *a* activity.[25] Since ATP and glucose 6-phosphate interact noncovalently with muscle phosphorylase *b* to inhibit its activity, and 5′-AMP and inorganic phosphate (which is also a substrate for the reaction) stimulate phosphorylase *b* activity,[26,27] the changes observed in hypoxic rat hearts indicated that stimulation of phosphorylase *b* activity would be an alternative mechanism to converting phosphorylase *b* to *a* for "turning on" glycogenolysis.[25] The early studies on the phosphorylase kinase deficiency mutation have been interpreted to indicate that the lack of a phosphorylase *b* to *a* converting mechanism was compatible with an essentially normal life.[28]

Findings on recent studies using more sensitive techniques, however, showed that skeletal muscle extracts of I strain mice do contain small amounts of phosphorylase kinase activity (0.3 percent of

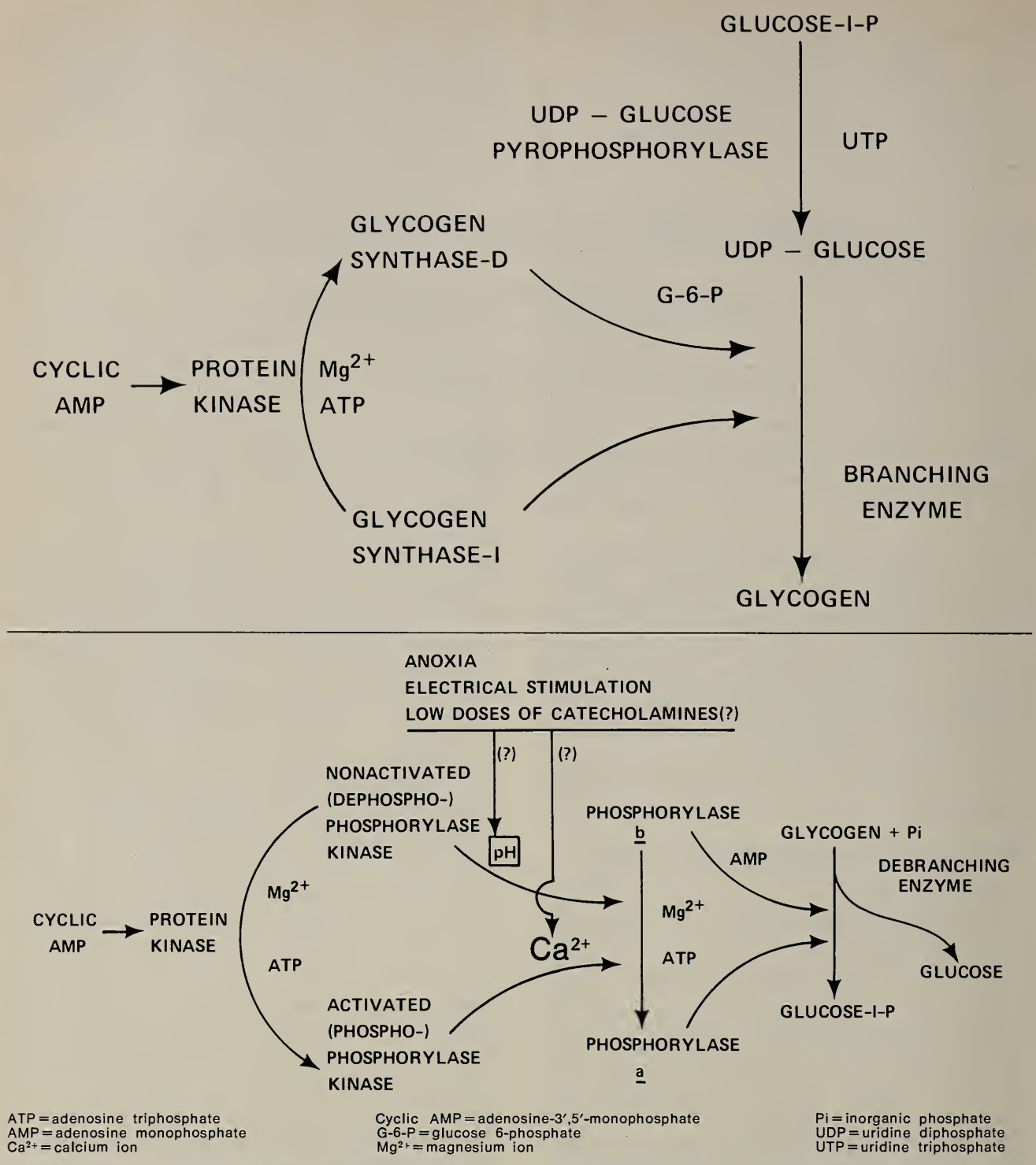


Figure 1.—Enzymatic pathways catalyzing the synthesis and degradation of glycogen. **Upper,** A detailed discussion of the regulation of glycogen synthesis may be found in Villar-Palasi and Larner.[2] **Lower,** The diagram of the glycogenolytic pathway is modified from Gross and Mayer.[3] In the glycogenolytic pathway experimental evidence has shown that anoxia, electrical stimulation and low doses of catecholamines control the catalytic activity of phosphorylase kinase in the absence of evidence for conversion of nonactivated to activated form.[4-6]

that of control strains),[29] as well as normal amounts of a protein that cross-reacts with antisera prepared against purified rabbit skeletal muscle phosphorylase kinase.[29,30] Incubation of I strain hemidiaphragms in oxygenated Krebs-Ringer bicarbonate buffer with either isoproterenol or epinephrine produced glycogenolysis, although the rate was less than that of control strain hemidiaphragms.[23,31] Catecholamines also were found to stimulate phosphorylase *b* to *a* conversion in I strain hemidiaphragms. There was a close correlation between the relative increase

TABLE 1.—*Human Glycogenoses*

Type	*Alternate Name*	*Enzyme Defect*	*Tissue Affected*	*Principle Clinical Features*
I	von Gierke's disease	Glucose 6-phosphatase	Liver, kidney, gut	Hepatomegaly, hypoglycemia, ketosis, acidosis
II	Pompe's disease	Lysosomal acid maltase (α-1,4-glucosidase)	Generalized	Cardiomegaly, heart failure, hepatomegaly, hypotonia; some adult cases with involvement of muscle and liver but without cardiomegaly
III	Limit dextrinosis	Debrancher enzyme (amylo-1,6-glucosidase)	Liver, heart, skeletal muscle	Moderate to marked hepatomegaly, none to moderate cardiomegaly; myopathies observed in some adults
IV	Amylopectinosis	Brancher enzyme (α-1, 4-glucan: α-1,4-glucan 6-glycosyl transferase)	Generalized	Hepato-splenomegaly, cirrhosis, ascites, liver failure
V	McArdle's disease	Muscle phosphorylase	Skeletal muscle	Temporary weakness and cramping of skeletal muscles after exercise, myoglobinuria
VI	Hers disease	Liver phosphorylase	Liver	Marked hepatomegaly
VII	....	Phosphofructokinase	Skeletal muscle, erythrocytes	Temporary weakness and cramping of skeletal muscle after exercise, pigmenturia
VIII	....	None yet demonstrated	Liver, brain	Hepatomegaly; neurologic deterioration progressing to decerebration and death
IX	....	Liver phosphorylase kinase	Liver	Marked hepatomegaly
X	....	Cyclic AMP-dependent protein kinase of skeletal muscle and presumably liver	Liver, skeletal muscle	Marked hepatomegaly

Adapted from Hug.[7]

in phosphorylase *a* activity and stimulation of glycogenolysis in I strain hemidiaphragms as compared with that of the control strain (C57BL).[23,31] These results suggest that catecholamines stimulate glycogenolysis in skeletal muscle of I strain, as in the control strain, by increasing phosphorylase *b* to *a* conversion. Future biochemical studies on human glycogenoses using more sensitive techniques may also indicate alternative interpretations of their biochemistry.

The genetic relationship of the phosphorylase kinase deficiency mutation in mice to those reported in humans is not clear. Huijing and Fernandes[32] reported a series of persons with a deficiency of phosphorylase kinase activity in leukocyte extracts. Of the 35 persons, 32 were male—suggesting that the defect is sex-linked, as is the murine phosphorylase kinase deficiency mutation.[22] Huijing and Fernandes[32] proposed that their subjects had a hepatic glycogenosis, although this was confirmed in only one case by assay of liver biopsy material. Consistent with their conclusion is the observation that leukocyte phosphorylase has properties similar to hepatic rather than skeletal muscle phosphorylase.[33] However, Hug and colleagues found that of their subjects who had a hepatic phosphorylase kinase deficiency confirmed by direct assay of biopsy material three of seven were females. Hepatic phosphorylase kinase activity is only slightly decreased in I strain mice to between 44 and 71 percent of that of control strains.[29,34]

Another complication is that studies of human hepatic glycogenoses have frequently failed to differentiate between deficiencies of phosphorylase and phosphorylase *b* to *a* converting activity.[12,17] Hepatic phosphorylase *b*, unlike that of muscle, is not fully active in the presence of saturating concentrations of 5′-AMP.[27] So to assay total activity in suspected glycogenoses, hepatic phosphorylase must be entirely converted to the *a* form by addition of phosphorylase kinase[12] or hepatic phosphorylase *b* may be assayed using 0.7 molar (M) sodium sulfate (Na_2SO_4) and 1 millimolar (mM) 5′-AMP.[35] Without an accurate determination of total phosphorylase activity, types VI and IX glycogenoses cannot be differentiated.

From the studies of glycogen storage conditions in mice several additional observations have been made that are relevant to the study of human glycogenoses.

• *To properly interpret biochemical studies of human skeletal muscle glycogenoses, it is necessary that control assays be carried out on muscle*

specimens matched for the age of the patient and the muscle type of the biopsy specimen.

While these precautions have been pointed out previously,[36,37] most studies still fail to report the age of the patient or muscle-type(s) used in control muscle samples. Illingworth[38] has argued that differences in enzyme activities between muscle types would not be of sufficient magnitude to be a factor in interpreting the results of biochemical studies of glycogenoses. However, when the enzymatic activities of the variant specimen are significantly above zero, the developmental state of the muscle and its type must be considered.

In Swiss-Webster mice at 6 to 8 days of age, the phosphorylase kinase activity of the gastrocnemius muscle was 12 percent of that of adults (Table 2), but even at 19 to 21 days of age, immediately before weaning, the activity was still only 38 percent of that of adults. Therefore, there was a slow postnatal increase in phosphorylase kinase activity in gastrocnemius muscle. In the diaphragm and soleus muscle the percent increase in phosphorylase kinase activity was less than in the gastrocnemius in the period examined. Total phosphorylase activity also slowly increased in developing mouse skeletal muscle (Table 2). Similar results on the development of skeletal muscle phosphorylase and phosphorylase kinase have been reported for the gastrocnemius of rats[40] and for abdominal and leg muscle of C57BL mice.[22] In rat liver there is a lesser postnatal increase in phosphorylase and phosphorylase kinase activity than in rat skeletal muscle.[40] The developmental patterns of the enzymes of glycogen metabolism have yet to be described in humans.

TABLE 2.—*Phosphorylase and Phosphorylase Kinase Activities of Three Skeletal Muscles of Young and Adult Mice*

Age	*Muscle*	*Phosphorylase Activity (units/gram)**	*Phosphorylase Kinase Activity (units/gram)†*
6-8 days . . .	gastrocnemius	9.2 ± 0.9	386 ± 34
	diaphragm	13.6 ± 1.5	332 ± 30
	soleus‡	8.0 ± 0.9	302 ± 24
19-21 days .	gastrocnemius	22.5 ± 3.7	1,259 ± 325
	diaphragm	13.5 ± 2.2	269 ± 20
	soleus	19.7 ± 3.9	1,031 ± 108
Adult	gastrocnemius	44.1 ± 4.5	3,282 ± 242
	diaphragm	17.7 ± 3.0	835 ± 136
	soleus	37.6 ± 4.9	1,440 ± 222

Skeletal muscle samples were homogenized in 10 volumes of 20 millimolar (mM) potassium fluoride (KF) and 4 mM ethylenediamine tetraacetic acid (EDTA), pH 7.4, and the 10,000×g (10 minutes) supernatant fraction was assayed for total phosphorylase activity in the presence of 2 mM 5′-adenosine monophosphate (AMP) and phosphorylase kinase activity at pH 8.2 as previously described.[29] Results are expressed as the mean ± standard error of the mean (SEM) of the values from four determinations on different litters at ages of 6 to 8 days and 19 to 21 days and from five determinations on adults (over 10 weeks of age). There was no statistically significant difference ($P>0.05$) in the protein contents of the supernatant fractions among the three age groups or among the three muscle types in adults.

*Unit = forms 1 μmole of glucose 1-phosphate per minute.[39]
†Unit = converts 1 unit of phosphorylase *b* to *a* per minute.[39]
‡At this age it was difficult to completely remove all of the gastrocnemius from the soleus sample so that the latter may be contaminated with the former.

The three muscles used in the study for Table 2 were selected because in rodents they represent three distinct types: fast twitch-white (gastrocnemius), fast twitch-red (diaphragm) and slow twitch-intermediate (soleus).[41,42] As Table 2 shows, the phosphorylase and phosphorylase kinase activities vary widely among the muscle types in adults with the diaphragm having activities of 40 percent and 25 percent, respectively, of that of gastrocnemius. These experiments show that under physiologic conditions murine skeletal muscle phosphorylase and phosphorylase kinase activities can vary up to ten fold depending on the age of the animal and the muscle type. Thus in biochemical studies of glycogenoses, control samples matched for age of the patient and muscle type are necessary for accurate interpretation of the data, unless the variant enzyme is devoid of activity.

• *Assays of mutant enzymatic activities* in vitro *under optimal conditions may not accurately correlate with* in vivo *activity.*

Skeletal muscle extracts of I strain gastrocnemius muscles convert purified rabbit skeletal muscle phosphorylase *b* to *a* at 0.3 percent of the rate of the enzyme from control strains (C57BL/St or Swiss-Webster) when assayed *in vitro* in dilute solution by conventional procedures.[29] Another system for measuring phosphorylase *b* to *a* conversion *in vitro* is the protein-glycogen complex isolated from skeletal muscle extracts by differential centrifugation.[10] Addition of ATP (10 mM), magnesium ion (Mg^{2+}) (50 mM), and calcium ion (Ca^{2+}) (4 mM) to the protein-glycogen complex isolated from Swiss-Webster mice produced conversion of 100 percent of the phosphorylase to the *a* form within 20 seconds.[29] In the I strain protein-glycogen complex under similar experimental conditions there was also a rapid phosphorylase *b* to *a* conversion, but only 11 percent phosphorylase *a* was pro-

duced.[29] This percent conversion of phosphorylase to the *a* form was the same as that observed in I strain diaphragms incubated with isoproterenol. So the phosphorylase *b* to *a* conversion in the protein-glycogen complex correlated more closely with the results in intact muscle than did the results of the conventional quantitative assays in dilute solution at apparently optimal conditions.[29]

A poor correlation of the enzyme deficiency measured at optimal assay conditions and the severity of the genetic disease has also been observed with several glucose 6-phosphate dehydrogenase (G6-PD) variants.[43] Patients with the Gd Union and Gd Mediterranean variants have G6-PD activities in their red blood cells of less than 5 percent of normal when assayed under optimal conditions and yet do not have chronic hemolytic anemia. This contrasts to subjects with the variants Gd Manchester and Gd Freiburg who have chronic hemolytic anemia but their G6-PD activities are 25 to 30 percent, and 10 to 20 percent of normal, respectively.[43] However, when these variant enzymes are assayed under simulated physiologic conditions (that is, with concentrations of substrates, activators and inhibitors found in red blood cells at pH 7.3), then the deficiencies in the enzyme activities correlate more closely with the severity of clinical disease.[43]

• *Multiple enzymatic deficiencies may occur as secondary effects of the primary lesion.*

Multiple deficiencies in enzymatic activities of glycogen metabolism have been frequently reported in human glycogenoses.[9,44] For example, there have been several persons found to be deficient in both debrancher enzyme and glucose 6-phosphatase activity.[8] The genetic implications of such multiple coinherited enzymatic deficiencies within any metabolic pathway are substantial and would argue strongly for an operon-type of genetic regulation in mammals. Alternative explanations are suggested from the results of studies in animals.

Secondary effects would result if the increased tissue glycogen concentration or deficiencies in the products of glycogenolysis altered the rate of synthesis or degradation of proteins. An apparent secondary effect of the phosphorylase kinase deficiency mutation is an increased total skeletal muscle phosphorylase activity (gastrocnemius) to a value of 60 percent greater than that of the C57BL strain.[29] The increase in total phosphorylase activity in I strain skeletal muscle may act to compensate for the decreased phosphorylase kinase activity. Mutations producing pronounced alterations in important metabolic pathways are likely to produce multiple secondary changes in the cellular physiology.[9]

Multiple enzymatic deficiencies could also result from mutations affecting a structural protein or altering a protein involved in the transduction of hormonal control of enzymes in the metabolic pathway. Studies on the mutations that produce a deficiency of hepatic glucose 6-phosphatase activity have shown multiple biochemical changes including notably decreased activities of tyrosine aminotransferase and serine dehydratase.[45] These mutants did not show a gene dosage effect for these abnormalities, that is, mice heterozygous for the mutant alleles could not be differentiated from those homozygous for the wild-type alleles. Furthermore, several of the mutant alleles showed complementation, that is, mice doubly heterozygous for certain combinations of the separate mutant alleles were viable and showed essentially normal neonatal hepatic glucose 6-phosphatase activities.[45] These results indicate that these alleles at the albino locus do not code for the structural gene for glucose 6-phosphatase.

Studies on ultrastructural changes in the glucose 6-phosphatase deficiency mutations have shown severe abnormalities of the hepatic endoplasmic reticulum membranes and Golgi apparatus.[46] Since glucose 6-phosphatase is localized in microsomal membranes, structural changes in these membranes could notably reduce its activity. However, neither hepatic tyrosine aminotransferase nor serine dehydratase is a microsomal enzyme, so that altered microsomal structure cannot entirely explain the multiple effects. The activities of all three enzymes can, however, be induced in normal mice by administration of hormones or by dietary factors, and cyclic AMP is thought to be a common intermediary in these enzyme inductions. Since these inductions do not occur in the mutant animals,[21,47] it has been suggested that an alteration in one of the proteins involved in the transduction of the hormonal response might be the primary defect.[47] Thus, there are several alternative explanations to an operon-like hypothesis for multiple enzymatic deficiencies in a metabolic pathway.

• *The lack of a cross-reacting protein to an antiserum produced to the normal enzyme does not necessarily show that the mutation results in the absence of the mutant enzyme in the tissue.*

Analyses of tissue extracts of mutations affecting enzymes frequently include a test for cross-reacting material to an antiserum prepared against the normal enzyme.[48,49] The presence of cross-reacting material indicates the presence of an enzyme with an altered structure. However, the lack of cross-reacting material does not necessarily show that there is an absence of a structurally altered enzyme. For example, tests for cross-reacting material in I strain skeletal muscle extracts were conducted with antisera prepared in goats and guinea pigs to purified rabbit skeletal muscle phosphorylase kinase. The antiserum prepared in guinea pigs cross-reacted with normal mouse phosphorylase kinase but not with I strain muscle extracts when tested by double diffusion in agar (Figure 2) or quantitative precipitation assays (Gross SR, Longshore MA and Pangburn S, unpublished observations). With goat antiserum, cross-reacting material was found in I strain extracts with both techniques (Figure 2).[29] It has now been recognized in several systems that antibodies may or may not bind antigens that are structurally related to the antigen.[50] Hence, mutant tissue extracts should be tested with several different antisera prepared against the normal enzyme in species that are not closely related. Only then is a lack of cross-reactivity in the mutant tissue likely to be significant. It is important for understanding the mechanisms regulating genetic expression in mammalian systems to differentiate between mutations that result in a complete absence of enzyme and those that result in an extensively modified protein.

Summary

The paucity of animal models of human glycogen storage conditions substantially restricts the use of experimental models to obtain information relevant to human disease. Studies on two such animal models with glycogen storage, the phosphorylase kinase and glucose 6-phosphatase deficiencies in mice, have indicated important principles that may be applicable to the elucidation of the biochemical and molecular bases of human glycogenoses and to their diagnosis.

- Control specimens should be matched for the age of patient and, if a skeletal muscle biopsy specimen, for the muscle type to allow accurate interpretation of the biochemical data obtained in biopsy material from patients with a glycogenosis.
- Enzymatic assay conditions *in vitro* should attempt to simulate conditions in intact tissue, especially with respect to concentrations of substrates and inhibitors. This also aids in the interpretation of the biochemical data.
- Changes in more than one enzymatic activity may be observed in affected patients. This may complicate both the diagnosis and attempts to un-

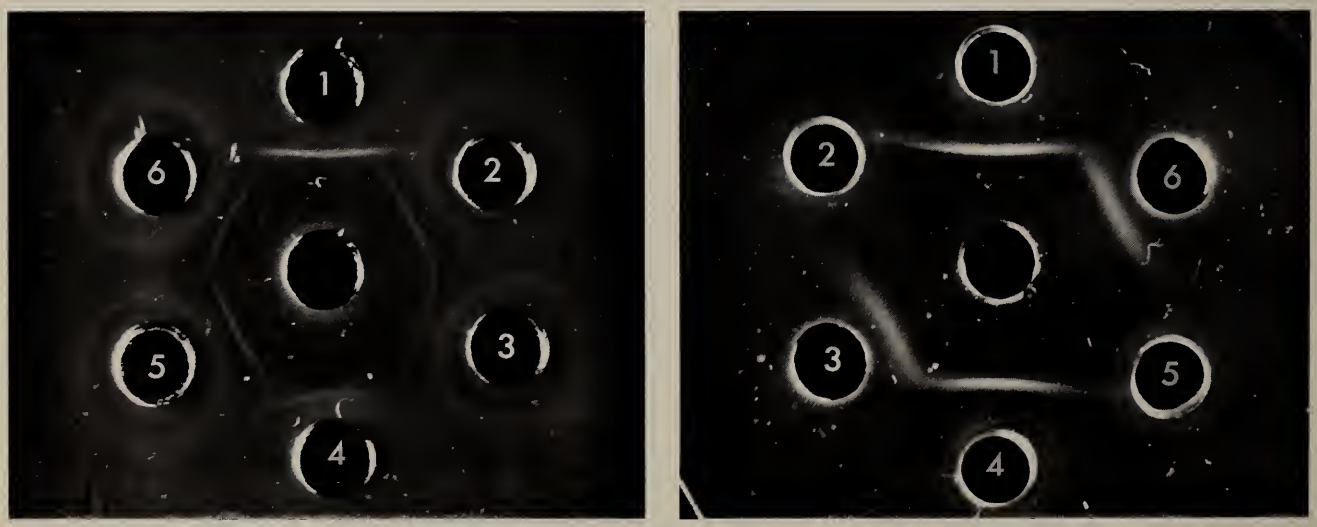


Figure 2.—Differential Cross-Reactivity of I Strain Phosphorylase Kinase with Antiphosphorylase Kinase Sera Prepared in Goats and Guinea Pigs. Ouchterlony double diffusion analysis was done by incubating the agar plates for 3 to 4 days in a humidified atmosphere at room temperature. **Center well, Left,** goat antiserum to rabbit muscle phosphorylase kinase; **Right,** guinea pig antiserum to rabbit phosphorylase kinase. **Outside wells 1** and **4,** rabbit muscle phosphorylase kinase (40 pellet fraction prepared as described by Krebs and co-workers[51]) 200 μg of protein except in **well 4** at left (100 μg); **2** and **5,** 40 pellet fraction from skeletal muscle of I strain mice,[29] 1 mg protein; **3** and **6,** 40 pellet fraction from skeletal muscle of Swiss-Webster mice,[29] 1 mg protein. The antisera were prepared to purified rabbit phosphorylase kinase (Peak II, with the method of Hayakawa and co-workers[52]) as previously described.[29,53]

derstand the nature of the primary defect. Multiple enzymatic deficiencies may occur where the primary mutation alters the cellular structure or proteins necessary for the transduction of hormonal signals. In addition, enzymatic activities may decrease or increase secondary to an alteration in cellular function that changes the rate of synthesis or degradation of multiple proteins.

- Immunochemical studies of tissue extracts from affected patients should use antisera made in several divergent species, if the results of the initial studies with a single antiserum show a lack of cross-reactivity. This would provide more substantial evidence to differentiate whether the mutant tissue extract lacks the mutant enzyme or has an extensively modified enzyme.

It is hoped that future studies on glycogen storage conditions in experimental animals will not only provide additional information on the points raised here but will also describe new areas of importance for the understanding of human glycogenoses.

REFERENCES

1. Cori CF, Schmidt G, Cori GT: The synthesis of a polysaccharide from glucose-1-phosphate in muscle extract. Science 89:464-465, 1939
2. Villar-Palasi C, Larner J: Glycogen metabolism and glycolytic enzymes. Ann Rev Biochem 39:639-672, 1970
3. Gross SR, Mayer SE: Phosphorylase kinase mediating the effects of cyclic AMP in muscle. Metab 24:369-380, 1975
4. Stull JT, Mayer SE: Regulation of phosphorylase activation in skeletal muscle *in vivo*. J Biol Chem 246:5716-5723, 1971
5. Drummond GI, Harwood JP, Powell CA: Studies on the activation of phosphorylase in skeletal muscle by contraction and by epinephrine. J Biol Chem 244:4235-4240, 1969
6. Dobson JG Jr, Mayer SE: Mechanisms of activation of cardiac glycogen phosphorylase in ischemia and anoxia. Circ Res 33:412-420, 1973
7. Hug G: Nonbilirubin genetic disorders of the liver, *In* Gall EA, Mostof FK (Eds): The Liver. International Academy of Pathology Monograph No. 13. Baltimore, The Williams and Wilkens Co., 1973, pp 21-71
8. Brown BI, Brown DH: Glycogen-storage diseases: types I, III, IV, V, VII and unclassified glycogenoses, *In* Dickens F, Randle PJ, Whelan WJ (Eds): Carbohydrate Metabolism and Its Disorders. New York, Academic Press, 1968, pp 124-150.
9. Howell RR: The glycogen storage diseases, *In* Stanbury JB, Wyngaarden JB, Fredrickson DS (Eds): The Metabolic Basis of Inherited Disease. New York, McGraw-Hill, 1972, pp 149-173
10. Fischer EH, Heilmeyer LMG Jr, Haschke RH: Phosphorylase and the control of glycogen degradation. Curr Topics in Cell Regulat 3:211-251, 1971
11. Krebs EG: Protein kinases. Curr Topics in Cell Regulat: 5:99-133, 1972
12. Hug G, Schubert WK, Chuck G: Deficient activity of dephosphorylase kinase and accumulation of glycogen in the liver. J Clin Invest 48:704-715, 1969
13. Hug G, Schubert WK, Chuck G: Loss of cyclic 3′,5′-AMP dependent kinase and reduction of phosphorylase kinase in skeletal muscle of a girl with deactivated phosphorylase and glycogenosis of liver and muscle. Biochem Biophys Res Commun 40:982-988, 1970
14. Newsholme EA, Randle PJ, Manchester KL: Inhibition of phosphofructokinase reaction in perfused rat heart by respiration of ketone bodies, fatty acids and pyruvate. Nature 193:270-271, 1962
15. Layzer RB, Rowland L, Ranney HM: Muscle phosphofructokinase deficiency. Arch Neurol 17:512-523, 1967
16. Kemp RG: Rabbit liver phosphofructokinase: comparison of some properties with those of muscle phosphofructokinase. J Biol Chem 246:245-252, 1971
17. Hers HG, van Hoof F: Glycogen storage diseases: type II and type VI glycogenosis, *In* Dickens F, Randle PJ, Whelan WJ (Eds): Carbohydrate Metabolism and Its Disorders, Vol 2. New York, Academic Press, 1968, pp 151-168
18. Engel AG: Acid maltase deficiency in adults—Studies in four cases of a syndrome which may mimic muscular dystrophy or other myopathies. Brain 93:599-616, 1970
19. Erickson RP, Gluecksohn-Waelsch S, Cori CF: Glucose-6-phosphatase deficiency caused by radiation-induced alleles at the albino locus in the mouse. Proc Natl Acad Sci 59:437-444, 1968
20. Lyon JB Jr, Porter J: The relation of phosphorylase to glycogenolysis in skeletal muscle and heart of mice. J Biol Chem 238:1-11, 1963
21. Gluecksohn-Waelsch S, Cori CF: Glucose-6-phosphatase deficiency: mechanisms of genetic control and biochemistry. Biochem Genet 4:195-201, 1970
22. Lyon JB Jr: The X-chromosome and the enzymes controlling muscle glycogen: phosphorylase kinase. Biochem Genet 4:169-185, 1970
23. Gross SR, Longshore MA: Epinephrine-stimulated glycogenolysis in skeletal muscle of mice with the phosphorylase *b* kinase deficiency mutation. Proc Western Pharmacol Soc 17:125-128, 1974
24. Danforth WH, Lyon JB Jr: Glycogenolysis during tetanic contraction of isolated mouse muscles in the presence and absence of phosphorylase *a*. J Biol Chem 239:4047-4050, 1964
25. Morgan HE, Parmeggiani A: Regulation of glycogenolysis in muscle—II. Control of glycogen phosphorylase reaction in isolated perfused heart. J Biol Chem 239:2435-2439, 1964
26. Helmreich E: Allosteric control of muscle phosphorylase. FEBS Symposium 19:131-148, 1969
27. Fischer EH, Pocker A, Saari JC: The structure, function and control of glycogen phosphorylase, *In* Campbell PW, Dickens F (Eds): Essays in Biochemistry. New York, Academic Press, 1970, pp 23-68
28. Cohen P: The role of phosphorylase kinase in the nervous and hormonal control of glycogenolysis in muscle. Biochem Soc Symp 39:51-73, 1974
29. Gross SR, Mayer SE: Characterization of the phosphorylase *b* to *a* converting activity in skeletal muscle extracts of mice with the phosphorylase *b* kinase deficiency mutation. J Biol Chem 249: 6710-6718, 1974
30. Cohen PTW, Cohen P: Skeletal muscle phosphorylase kinase deficiency: detection of a protein lacking any activity in ICR/IAn mice. Fed Europ Biol Soc Lett 29:113-116, 1973
31. Gross SR, Longshore MA: Relationship of cyclic AMP concentration, phosphorylase *b* to *a* conversion, and glycogenolysis in skeletal muscle of phosphorylase kinase deficient mice. Proc 2nd Intl Conf Cyclic AMP 36, 1974
32. Huijing F, Fernandes J: X-Chromosomal inheritance of liver glycogenosis with phosphorylase kinase deficiency. Am J Human Genet 21:275-284, 1969
33. Proux D, Dreyfus J-C: Phosphorylase isozymes in tissues —Prevalence of the liver type in man. Clin Chim Acta 48:167-172, 1973
34. Hornbrook KR, Lyon JB Jr: The regulation of glycogen metabolism in mouse liver. Biochim Biophys Acta 215:29-38, 1970
35. Appelman MM, Krebs EG, Fischer EH: Purification and properties of inactive liver phosphorylase. Biochemistry 5:2101-2107, 1966
36. Schapira G, Dreyfus J-C, Schapira F: Biochemistry of striated muscle during human muscular diseases. Enzym Biol Clin 11:8-31, 1970
37. Krebs EG: *In* Whelan WJ, Cameron MP (Eds): General Discussion in Control of Glycogen Metabolism. Boston, Little Brown and Co., 1964, p 399
38. Illingworth B: *In* Whelan WJ, Cameron MP (Eds): General Discussion in Control of Glycogen Metabolism. Boston, Little Brown and Co., 1964, p 399
39. Mayer SE, Krebs EG: Studies on the phosphorylation and activation of skeletal muscle phosphorylase and phosphorylase kinase *in vivo*. J Biol Chem 245:3153-3160, 1970
40. Novak E, Drummond GI, Skala J, et al: Developmental changes in cyclic AMP, protein kinase, phosphorylase kinase, and phosphorylase in liver, heart, and skeletal muscle of the rat. Arch Biochem Biophys 150:511-518, 1972
41. Close RI: Dynamic properties of mammalian skeletal muscles. Physiol Rev 52:129-197, 1972
42. Barnard RJ, Edgerton VR, Furukawa T, et al: Histochemical, biochemical, and contractile properties of red, white, and intermediate fibers. Am J Physiol 220:410-414, 1971
43. Yoshida A: Hemolytic anemia and G6PD defiiciency. Science 179:532-537, 1973
44. Auerbach VH, DiGeorge AM: Genetic mechanisms producing multiple enzyme defects—A review of unexplained cases and a new hypothesis. Amer J Med Sci 249:718-747, 1965
45. Gluecksohn-Waelsch S, Schiffman MB, Thorndike J, et al: Complementation studies of the lethal alleles in the mouse causing deficiencies of glucose-6-phosphatase, tyrosine aminotransferase, and serine dehydratase. Proc Natl Acad Sci 71:825-829, 1974
46. Trigg MJ, Gluecksohn-Waelsch S: Ultrastructural basis of biochemical effects in a series of lethal alleles in the mouse: neonatal and developmental studies. J Cell Biol 58:549-563, 1973
47. Diamond RP, Erickson RP: Gene dosage in a deletion for a nuclear-coded mitochondrial enzyme. Nature 248:418-419, 1974
48. Dreyfus J-C, Proux D, Alexandre Y: Molecular studies on glycogen storage diseases. Enzyme 18:60-72, 1974
49. Robbins PW: Immunological study of human muscle lacking phosphorylase. Fed Proc 19:193, 1960
50. Richards FF, Konigsberg WH, Rosenstein RW, et al: On the specificity of antibodies. Science 187:130-137, 1974
51. Krebs EG, Love DS, Bratvold GE, et al: Purification and properties of rabbit skeletal muscle phosphorylase *b* kinase. Biochemistry 3:1022-1033, 1964
52. Hayakawa T, Perkins JP, Walsh DA, et al: Physicochemical properties of rabbit skeletal muscle phosphorylase kinase. Biochemistry 12:567-573, 1973
53. Gross SR, Mayer SE: The phosphorylation of troponin B by phosphorylase *b* kinase in skeletal muscle of mice carrying the phosphorylase *b* kinase deficiency gene. Biochem Biophys Res Commun 54:823-830, 1973

Specialty Conference

Moderator:
THOMAS T. YOSHIKAWA, MD

Discussants:
MILAN FIALA, MD
PETER V. D. BARRETT, MD
JOHN H. WALSH, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Refer to: Yoshikawa TT, Fiala M, Barrett PVD, et al: Viral hepatitis—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 123:202-210, Sep 1975

Viral Hepatitis

THOMAS T. YOSHIKAWA, MD:* *The identification of Australia antigen (hepatitis B antigen* [HB Ag] *or hepatitis-associated antigen* [HAA]*) by Blumberg in 1965*[1] *provided great interest and new approaches to studying the clinical, pathological, epidemiological and immunological aspects of viral hepatitis. From the vast accumulation of data from investigators all over the world, it has become apparent that our traditional concept of viral hepatitis as "infectious" versus "serum" is no longer tenable. The causes of presumed "viral" hepatitis may be several; the clinical picture and natural history of this disease may vary considerably; the immunoserological data potentially have great diagnostic, epidemiologic and preventive significance.*

To provide a contemporary overview on the status of viral hepatitis, we are privileged to have three guest speakers who have spent much of their medical careers in studying this disease entity. Dr. Milan Fiala will discuss the viral causes of hepatitis and the morphology of hepatitis A and B viruses. This will be followed by a discussion on the clinical diagnosis, histopathology and natural history of viral hepatitis given by Dr. Peter Barrett. Concluding the symposium will be Dr. John Walsh who will speak on the serological and epidemiological aspects of hepatitis antigens.

Viral Causes of Hepatitis

MILAN FIALA, MD†

ACUTE, so-called viral hepatitis has been recognized as having two distinct clinical and epidemiological forms, viral hepatitis type A and type B. Each of these is thought to be caused by a different viral agent; the former by the elusive hepatitis A virus (HAV) which may be identical to the recently described parvovirus-like antigen,[2] and the latter by hepatitis B virus (HBV) which has been associated with the hepatitis B antigen (HB Ag).[3-6] Nevertheless, a difference in the host-response or the route of infection rather than in the viral agent has not been completely excluded as the cause of some or all of the differences between hepatitis type A and type B.[7,8] Different clinical manifestations associated with HB Ag are thought to be primarily related to variation in host-response to HBV, although variation in the pathogenic potential of different subtypes may not have been fully appreciated as yet.[9,10]

Other viral agents may cause hepatitis, in particular cytomegalovirus[11,12] and Epstein-Barr virus (EBV).[13] These two viruses, particularly the latter, have been classically associated with the

*Division of Infectious Diseases, Harbor General Hospital; Assistant Professor of Medicine, UCLA School of Medicine.

†Division of Infectious Diseases, Harbor General Hospital; Assistant Professor of Medicine, UCLA School of Medicine.

Reprint requests to: Division of Infectious Diseases, Department of Medicine, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

ABBREVIATIONS USED IN TEXT

anti-HBs = antibody to hepatitis B surface antigen
anti-HBc = antibody to hepatitis B core antigen
CAgH = Chronic aggressive hepatitis
CPH = Chronic persistent hepatitis
DNA = deoxyribonucleic acid
EBV = Epstein-Barr virus
HAA = hepatitis-associated antigen
HAV = hepatitis A virus
HB Ag = hepatitis B antigen (Australia antigen)
HBc Ag = hepatitis B core antigen
HBs Ag = hepatitis B surface antigen
HBV = hepatitis B virus
RNA = ribonucleic acid

infectious mononucleosis syndrome (that is, fever, malaise, atypical lymphocytosis, splenomegaly and lymphadenopathy). Although hepatic involvement can occur, overt clinical jaundice is uncommon. Recently, EBV has been associated with a fatal lymphoproliferative disease in four male cousins in which heavy lymphocytic infiltration of the portal areas of liver, hepatomegaly and striking abnormalities on liver function tests[14] were found. Herpes simplex and yellow fever viruses cause hepatitis which is, however, usually not the presenting feature. Influenza B and varicella-zoster viruses have been associated with Reye's syndrome[15] (encephalopathy and fatty degeneration of liver and other organs), but the pathogenetic relationship of these viruses to hepatic abnormalities remains unclear.

Hepatitis A Virus

In human volunteer experiments, this virus has been found resistant to ether and low pH, and passes through a filter of 100 nanometer (nm) pore size. Although many candidate agents isolated in cell culture[16] or in marmosets[17] have been proposed as HAV, until recently, none has been definitely linked with hepatitis A by seroepidemiological studies.

Recently, a transmissible agent isolated in marmosets (CR 326) has been proposed as being etiologically related to hepatitis A in man. In all eight subjects with hepatitis A, neutralizing antibodies to this virus developed during the illness.[18]

Using immune electron microscopy, spherical 27 nm particles were found in stools of hepatitis A patients in the acute phase of the disease. Patients with hepatitis A, acquired either experimentally or naturally, showed antibody response to this virus as shown by electron-dense coating and aggregation of these particles after incubation with patient sera. This virus resembles morphologically the agent of acute infectious gastroenteritis and appears to belong to the class of viruses known as parvoviruses.[2]

Hepatitis Type B Virus

Three morphologically-different but antigenically related particles are found in blood of patients infected with hepatitis type B virus: (1) spherical particles 20 nm in diameter (the vast majority of HB Ag particles); (2) spherical Dane particles 40 to 45 nm in diameter with a central core of 28 nm diameter; (3) tubular particles 30 to 700 nm long.

HB Ag and the core of the Dane particle are immunologically distinct: Antibody to HB Ag reacts with the outer membrane but not the inner core of the Dane particle.[19] The inner core is electron-dense when stained with uranyl acetate, suggesting the presence of nucleoprotein.[20] Hirschman and co-workers found evidence of deoxyribonucleic acid (DNA) polymerase activity in HB Ag which was thought to be dependent on an endogenous ribonucleic acid (RNA) template.[21] Using preparations of HB Ag rich in Dane particles, Kaplan and associates[22] found evidence for a DNA template within Dane particles based upon inhibition of DNA polymerase with Actinomycin D.

With the aid of direct immunofluorescent technique, two antigenic components of HBV have been shown; one occurs in the cytoplasm of hepatocytes, the other in their nuclei.[23] Following the demonstration of antigenic identity of cytoplasmic antigen with the 20 nm particles, rod-shaped forms and the coat of the Dane particle, and that of nuclear antigen with the core of Dane particle, the synthesis of HBV became better understood.[24] It is believed that the core of the Dane particle which may contain a DNA genome is made in the nuclei of hepatocytes. Virus capsid material is synthesized in the cytoplasm of liver cells in great excess. Only a very small portion of the capsid material is used up to coat the core of the Dane particle, whereas the majority is released in blood where it is present as 20 nm spherical particles or long rod-like particles, the ratio of which may depend upon pH and other

physicochemical conditions.[25] Virus particles are demonstrable in the nuclei of hepatocytes by electron microscopy.[26]

Although HBV is in general very resistant to various physical and chemical methods of inactivation, heating a 1:10 dilution of HB Ag positive serum for one minute at 98°C (208.4°F) modifies the infectivity of HBV without altering its antigenicity and immunogenicity.[27] A practical method of safeguarding serum for intravenous therapy may be a combined treatment with ultraviolet radiation and Beta-propiolactone.[28] After cold ethanol (Cohn) fractionation, HB Ag is distributed in all fractions except in gamma globulin.[29] Although it is present in only low titer in fractions I (fibrinogen, factor VIII) and V (crude albumin), the former fraction is highly icterogenic whereas the latter rarely, if ever, transmit HBV.

Treatment of HB Ag with ether reduces the particle size and increases its buoyant density;[30] however, it does not destroy the infectivity or antigenicity of HBV. Surface lipid may be also removed by chloroform-methanol (2:1, v/v) and sodium deoxycholate treatment without altering antigenicity.[31] Antigenically, HB Ag is a complex consisting of a common antigenic determinant *a*, and two subtype-specific determinants: either *d* or *y*,[32,33] and either *w* or *r*.[34] Virus phenotypes are designated as subtypes: *d* (adw); *y* (ayw); *r* (adr). The geographical distribution of virus subtypes is distinct for each subtype, though two or more subtypes share certain geographical areas. The spread of the *y* subtype appears to be linked with drug abuse.[10] This will be more extensively commented upon by Dr. Walsh. Additionally, a new set of antigenic determinants, *e*-complex, has been described that is physically distinct from the molecules carrying other previously-described HB Ag determinants.[35]

In the convalescent phase of hepatitis type B, hepatitis B antibody response (against the HB Ag) has been difficult to show by an agar gel diffusion test but it is readily shown by a sensitive test such as hemagglutination-inhibition or radioimmunoassay.[36] The antibody is probably boosted by subclinical infections. Its presence is higher among those groups of donors who have a higher than average carrier-rate of HB Ag.

Antibody against the Dane core is acquired in acute viral hepatitis 12 to 20 weeks after exposure, usually during or shortly after onset of antigenemia and well before the appearance of anti-HB Ag. Anti-core antibodies are found in chronic HB Ag carriers.[37] Doctor Walsh will further elaborate upon this topic.

Clinical and Pathological Findings and Sequelae of Viral Hepatitis

PETER V. D. BARRETT, MD*

As with any type of medical management, accurate diagnosis is the first step. However, in the case of hepatitis, we do not have the degree of diagnostic precision we would like, and consequently we sometimes spend almost as much time sorting out the different types of hepatitis as we spend actually managing them. A correct diagnosis is vital because nothing but symptomatic expectant care is indicated for most of the types of hepatitis, but for some types of chronic hepatitis, prednisone therapy with all of its attendant risks is indicated.

*Associate Chief, Division of Gastroenterology, Harbor General Hospital; Associate Professor of Medicine, UCLA School of Medicine.

The sorting out process that I alluded to is partly real and partly semantic. In a recent publication, 47 different terms were listed which have been used to describe chronic hepatitis and its variants.[38] This confusing abundance of terms evolved primarily as a result of attempts by many different groups of investigators to classify the histopathologic features and correlate them with clinical findings. More experience with liver biopsy specimen interpretation and in particular, the discovery of Australia antigen has produced considerable clarification of our concepts.

In acute viral hepatitis, the prodromal period of fatigue, malaise and anorexia is usually one to two weeks, following which jaundice may occur and persist for several more weeks. Complete biochemical and symptomatic recovery should occur in less than three months. Occasionally a patient will suffer a brief biochemical or symptomatic relapse within this three month period, but this usually does not indicate the presence of chronic

hepatitis. In general, transaminase and bilirubin concentrations are higher in patients with hepatitis B than in those with hepatitis A, but there is so much overlap in these test values that this information cannot be used as a differential diagnostic aid.[39]

Complete resolution of the hepatic process occurs in the vast majority of patients. We know that patients admitted to hospital with hepatitis represent only the tip of the iceberg, and that a great deal of hepatitis in the community is unrecognized. However, of the group in hospital, perhaps in as many as 10 percent, more severe variants of hepatitis develop or progress into a chronic form.

In the accompanying two figures (Figures 1 and 2), I have attempted to illustrate schematically the various clinical courses which can occur with acute hepatitis, and also the various types of chronic hepatitis as they are now understood. One of the severe variants of acute hepatitis has been termed submassive collapse, or subacute hepatic necrosis. The prodromal period and symptom complex seen in this group of patients

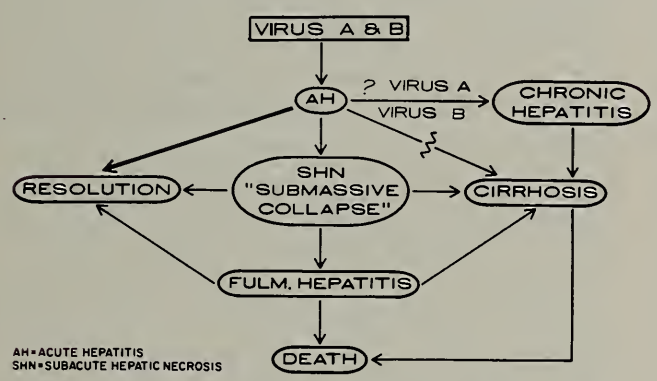


Figure 1.—Schematic representation of the sequelae of acute viral hepatitis.

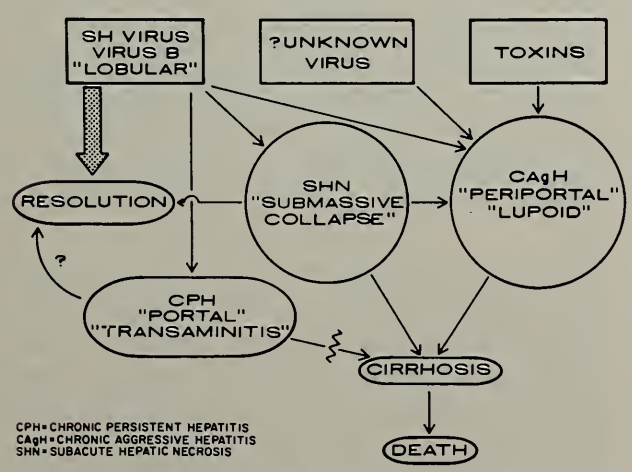


Figure 2.—Types of chronic hepatitis.

are often similar to those in patients in whom simple acute viral hepatitis develops, although in some the prodrome may be prolonged and insidious. The pathologic changes are also similar to those found in the simple acute form of hepatitis, but are exaggerated. Boyer and Klatskin have described changes in this variant which include bridging of connective tissue between central and portal areas, thus providing a basis for the architectural distortion and cirrhosis which occurs in some of these cases.[40] Fulminant hepatitis represents an even more severe clinical and pathological expression of this process and carries with it a mortality rate of 40 to 90 percent.[41]

Typically, peak transaminase values of 400 to 2,000 units are found at about the time of entry for patients admitted to hospital with hepatitis, and within two weeks of the onset of jaundice the values begin to fall at a rate of about 30 to 50 percent per week. Therefore, within three months after the onset of symptoms, results of liver function tests in the great majority of patients have returned to normal. However, in an occasional patient transaminase values are found which are persistently abnormal at a low-grade level. Overall, in probably 5 to 15 percent of patients in hospital with hepatitis, the disease follows this pattern, and in most of them the course and prognosis are benign, giving rise to the tongue-in-cheek description of transaminitis, emphasizing the benign nature of this form of chronic hepatitis. However, in not all patients with persisting transaminase abnormalities is there such an unremarkable course, and in perhaps as many as 3 percent[42] there is a more aggressive, symptomatic course which clearly compromises the prognosis.

On the one hand, chronic persistent hepatitis (CPH), or transaminitis, is a benign process which is usually asymptomatic, and is characterized biochemically by mild elevations of transaminases and pathologically by a sprinkling of lymphocytes in portal tracts. On the other hand, chronic aggressive hepatitis (CAGH) is usually symptomatic with remissions and relapses, and is characterized biochemically by more significant liver function test abnormalities, and pathologically by inflammatory cells, necrosis, fibrosis and sometimes cirrhosis. The distinction between CPH and CAGH is more than academic, because it has now been shown by several groups that survival in patients with CAGH is significantly prolonged by treatment with prednisone, while treatment is unnecessary in CPH.

Infections with hepatitis A virus or hepatitis B virus account for most cases of acute viral hepatitis, but the cause of chronic hepatitis is a more complicated issue. There is indirect evidence which suggests that HAV infection seldom results in the more severe variants of hepatitis, or chronic hepatitis, but substantiation of this concept must await the development of satisfactory serologic tests. In contrast, HBV is known to produce the entire spectrum of hepatitis, including fulminant hepatitis, CPH, CAGH and cirrhosis.

The histopathologic features of CAGH are usually not difficult to recognize, but it must be borne in mind that the liver has a limited repertoire with respect to the responses it can make to various insults. Thus, the microscopic appearance of CAGH in the liver of a patient in whom HBV infection is known to exist cannot be distinguished from the features seen in patients taking certain drugs (oxyphenisitin, methyldopa), or in patients with lupoid hepatitis which is not thought to be related to HBV.[43] Rarely, other diseases, such as Wilson's disease, can produce the same pathologic changes.

Treatment of acute and chronic hepatitis is frustrating both for physician and for patient because we have not yet found a specific drug which we can direct toward the hepatitis virus. In acute benign viral hepatitis, there is no evidence that dietary manipulations, corticosteroid therapy or even bedrest affect the course of the disease, and we therefore are left with only nonspecific supportive measures to treat patients. For the most severe variants of viral hepatitis, such as submassive collapse and fulminant hepatitis, corticosteroids are widely used despite the lack of convincing evidence of their efficacy. However, our therapeutic approach is on firmer footing when we deal with symptomatic patients with CAGH. Most patients with this problem, termed chronic active liver disease by the Mayo Clinic group, have been shown to respond to long-term prednisone treatment both clinically and pathologically. Azathioprine has also been studied by this group, but this drug does not appear to have a beneficial effect when used without prednisone.[44]

Viral hepatitis is a vexing and complicated problem, and it is one which is growing more complex each year. I hope that my remarks about some current clinical concepts have provided some perspective for this most important disease entity.

Serology and Epidemiology

JOHN H. WALSH, MD*

SEROLOGICAL TESTING for hepatitis traces its origin to precipitin reactions in agar gel involving antibody from multiple transfused subjects and antigen found in occasional persons. The antigen (Australia antigen) first was identified by Blumberg[1,45] in patients with leukemia and with Down's syndrome. Prince[46] and Gocke[47] subsequently identified similar antigens in patients with hepatitis; then it was appreciated that all three groups were working with the same system. The antigen was originally called Australia antigen, then hepatitis-associated-antigen, then hepatitis B antigen. Its occurrence in patients with hepatitis has been well documented.[48] More than one type of particle can be identified by electron microscopy. Doctor Fiala referred to the Dane particle[49] in his discussion as the 42 nm particle with a dense core. The antigen measured in ordinary serological tests for hepatitis is a surface antigen with a diameter of 22 nm composed of the coat of the presumed viral particle.[50] This now is known as hepatitis B surface antigen or HBs Ag. The core antigen is known as HBc Ag. Antibodies to the respective antigens are called anti-HBs and anti-HBc. The initials HBV are reserved for hepatitis B virus when it is definitely identified. This may or may not be identical with the Dane particle.

Subtypes of HB surface antigen were first described in detail by LeBouvier.[51] These were identified by observing spurring (evidence of partial identity) between different antigen-positive sera on agar gel diffusion. As previously mentioned, it is now generally accepted that there is a common antigen, known as *a* and two mutually exclusive additional antigenic determinants known as *d* and *y*.[52] Additional antigenic determinants known as *w* and *r* also have been described. Thus far all antigen found in the western world has been type *w* whereas *r* has been found in the Far East.[53]

Differences have been found in the geographical distribution of the *d* and *y* subtypes.[54] The *y* subtype predominates in the Mediterranean countries while *d* predominates in the Far East, Africa and South America. There is a mixed distribution

*Director of Gastroenterology Research, Division of Gastroenterology and Associate Professor of Medicine, UCLA School of Medicine.

in the United States and in Europe. Chronic carriers are more likely to be subtype *d* and acute cases are more commonly type *y*. This difference may reflect a relatively recent introduction of type *y*, especially among drug users. The subtypes are of some use epidemiologically, because infections always appear to breed true to the particular subtype of the infecting agent. Thus, all common source outbreaks are of the same subtype. Identification of a new subtype indicates an alternate source of infection. However, this marker is not of great practical value because of the limited number of subtypes. There is no definite clinical difference in the nature of the hepatitis induced by a particular subtype.

As briefly mentioned by Dr. Fiala, recently a newer antigen-antibody system has been described[55] which appears to be serologically and physicochemically distinct from HBs Ag and its subtypes. It has been designated as *e* antigen and *e* antibody. The presence of *e* antigen in the absence of *e* antibody correlated with chronic persistent or chronic aggressive hepatitis. Demonstration of *e* antibody without *e* antigen was found only in healthy blood donors without clinical, laboratory or histological evidence of hepatitis.

Serologic Methods for Detection of HBs Ag and Anti-HBs Ag

The *immunodiffusion* method is specific but not very sensitive and requires up to three days for optimal sensitivity.[56] Alternate tests have been developed to increase sensitivity and decrease incubation time, especially for the purpose of screening of donor blood samples. These have included a number of tests based on agglutination or precipitation. The most widely used of these tests is *counterelectrophoresis,*[57] which essentially is an agar gel diffusion augmented by passage of a current through the agar so that negatively charged antigen migrates toward the anode and crosses the antibody gamma globulin which migrates slightly toward the cathode. Both speed and sensitivity are increased by this test. *Complement fixation* has proved sensitive and specific for identification of hepatitis antigen.[58]

Hemagglutination tests[59] make use of red cells coated with antigen or antibody. In hemagglutination inhibition tests for HBs Ag, cells coated with purified hepatitis antigen are incubated with a fixed amount of antibody and unknown serum.[59] The presence of antigen in the serum inhibits the hemagglutination reaction. Direct hemagglutination of antigen coated cells has proved highly sensitive for detection of antibody to hepatitis B antigen. Various types of agglutination tests have been devised in which antibody is absorbed onto red blood cells[60] or other particles and hepatitis antigen causes agglutination of the particles.

These tests are relatively sensitive but they are not sensitive enough to detect the minimal known concentration of serum which can transmit hepatitis; in fact, serum diluted more than a thousandfold greater than the detection limits by complement fixation was capable of transmitting hepatitis in inoculation studies done a number of years ago.[61] This need for more sensitive tests led to the development of several forms of *radioimmunoassay*. The classical radioimmunoassay procedure involves competition between labeled antigen and unlabeled antigen, in standard or unknown solutions for a finite number of antibody binding sites. One early radioimmunoassay for HB Ag used paper chromatoelectrophoresis to separate antibody-bound from free labeled antigen.[62] A significant improvement in the separation system was made by several other groups who used a second antibody to precipitate antigen-antibody complexes.[63,64] This double antibody system has been especially sensitive for identification of antibody.[65]

A variant of radioimmunoassay was developed at Abbott Laboratories and is now used in a number of blood banks and by many investigators.[66] The principle of this assay is somewhat different. Test tubes are coated with antibody to hepatitis B antigen. Serum unknowns or standards are incubated in the coated tubes then washed out. Antigen present in the sample remains bound to the antibody on the wall of the tube. In the next step, labeled antibody is added to the tube; some of this labeled antibody becomes bound to other binding sites on the trapped antigen particles. The tubes are washed again and presence of antigen in the unknown sample is detected as residual radioactivity bound to the tube. This Ausria® test has proved easy to use but a number of laboratories have had problems with false positive reactions.[67-69] If a serum sample contains antibody directed against guinea pig serum, it will bind to the guinea pig anti-HB coating the tube. The other antibody binding site then will bind labeled guinea pig antibody added to the tube and produce a false positive reaction. A new experimental kit has been developed which uses human antibody to coat the tube and is said to produce significantly fewer false positive reactions.

Usefulness of HB Ag Testing in Blood Banks

Tests for HB antigen have had several clinical applications. The most widely used application has been for screening of blood donors. Several points can be made:

- Antigen positive blood carries a very high hepatitis risk: In approximately 70 percent of recipients of this blood, biochemical evidence of hepatitis will develop.[70]
- The more sensitive tests will identify from two to ten times as many positive units as agar gel diffusion.
- There is some question whether the additional positive units identified by the solid phase radioimmunoassay carry the same high risk of inducing hepatitis; in some cases this may be because of false positive tests.[71]
- The overall incidence of posttransfusion hepatitis has shown a modest but not overwhelming decrease since donor testing has become routine.[71]
- It has been estimated that approximately two thirds of cases of transfusion hepatitis are transmitted by blood that produces negative tests, either because the tests are not sensitive enough or because some other agent is responsible for the infection.[71]
- Antigen testing gives a reasonable indication of the quality of a whole population of blood donors as to hepatitis risk, even if individual units cannot always be identified. That is, donor populations with high rates of positive units also produce higher rates of hepatitis in recipients. In general, blood obtained from commercial blood banks is more likely to produce higher rates of hepatitis in recipients and have a higher rate of antigen-positive units than blood from the Red Cross or other voluntary sources.[72]
- On the other hand, there has been no proven association between transfusion of antibody to hepatitis antigen and development of hepatitis.[73]
- If there is a choice between using all volunteer-donated blood and antigen testing of commercial blood, untested volunteer blood is considerably safer than tested commercial blood.

Antibody to HBs Ag

Even with highly sensitive radioimmunoassay and hemagglutination tests for hepatitis B antibodies, the pattern of antibody and immunity is not completely defined.[74,75] One reason may be that HB antigen is not the whole virus. Thus, antibodies against the surface antigen may not provide a good indication of the status of immunity or exposure to the virus.

Antibody has been shown to occur regularly after exposure to the MS-2 strain of hepatitis B virus in studies done at Willowbrook Hospital in New York.[76] Other studies done after exposure to live hepatitis B virus at the same institution showed development of antibody in more than 80 percent of patients during the convalescent phase. It should be emphasized that these antibodies usually could not be shown by less sensitive techniques such as agar gel diffusion and complement fixation.

In transfusion hepatitis, the pattern has not been quite as clear. Using sensitive techniques, preexisting antibody can be shown in 10 to 20 percent of patients who receive transfusions. Occasionally in these patients, hepatitis will develop, possibly due to another agent.[77]

Detection of HBc Ag and Antibody

More recently a test has been developed by a group at the Division of Biologics Standards for detection of antibody to the core antigen.[37] This group purified core antigen obtained from an infected chimpanzee and used the antigen to develop a complement fixation test for anti-core antibody. They were able to demonstrate anti-core antibody during the acute phase of the disease, before demonstration of surface antibody. They also have found persistent anti-core antibody in chronic carriers of HB antigen, suggesting continued stimulation of antibody production by persistence of the virus. In patients who have recovered from hepatitis B infection, the core antibody seems to disappear. Therefore, presence of anti-core antibody appears to be indicator of ongoing or persistent viral replication.[78,79]

Detection of Hepatitis A Virus

The immune electron microscopic identification of hepatitis A virus particles in stool suspensions also has been used to show antibody to hepatitis A,[2] as previously mentioned by Dr. Fiala. Purification of a suitable amount of hepatitis A antigen should lead to a serological test for hepatitis A antibody. Such a test promises to offer specific identification of patients with infection due to this agent, similar to other tests which use paired acute and convalescent sera for diagnosis of viral illnesses.

Development of Hepatitis Vaccine

Inoculation studies have shown that experimental infection with either hepatitis A or hepatitis B produces a high degree of immunity to a second inoculation of the same agent within one to two years.[27] However, development of live vaccines will be extremely difficult since neither agent has been cultured successfully and there are no simple animal models in which to test attenuation.[80] The possibility of inducing chronic liver disease is a major theoretical hazard.

Vaccination with killed or inactivated hepatitis B antigen offers more promise in the short run. Krugman and co-workers have shown that brief boiling of infectious serum destroys infectivity but not antigenicity. After immunization with such a preparation, they showed significant resistance to infection with hepatitis B.[27]

A great deal of attention has been given to the possibility of preventing hepatitis with hyperimmune gamma globulin. Krugman showed either prevention or attenuation of hepatitis B infection in inoculated subjects who promptly received gamma globulin with a high titer of HB antibody.[81] Ordinary pooled gamma globulin has not been shown to have significant protective effects in similar studies or in patients receiving blood transfusion.[82] There are few data on the use of hyperimmune anti-HBs Ag.

REFERENCES

1. Blumberg BS, Alter HJ, Visnich S: A "new" antigen in leukemia sera. JAMA 191:541-546, Feb 1965

2. Feinstone SM, Kapikian AZ, Purcell RH: Hepatitis A: Detection by immune electron microscopy of a viruslike antigen associated with acute illness. Science 182:1026-1028, Dec 7, 1973

3. Blumberg BS, Sutnick AI, London WT, et al: The discovery of Australia antigen and its relation to viral hepatitis. Perspect Virol 7:223-240, 1971

4. Prince AM, Szmuness W, Hargrove RL, et al: The serum hepatitis virus specific antigen (SH): A status report. Perspect Virol 7:241-292, 1971

5. Krugman S, Giles JP: Viral hepatitis—A new light on an old disease. JAMA 212:1019-1029, May 11, 1970

6. Prince AM, Hargrove RL, Szmuness W, et al: Immunologic distinction between infectious and serum hepatitis. N Engl J Med 282:987-991, Apr 30, 1970

7. Editorial: Hepatitis viruses. Lancet 1:82-83, Jan 19, 1974

8. Sutnick AI, Senior JR, Goeser E, et al: Similarity of hepatitis following transfusion of Australia-antigen positive and negative blood. Lancet 2:461-464, Sep 1, 1973

9. Nielsen J, LeBouvier L: Subtypes of Australia antigen among patients and healthy carriers in Copenhagen. N Engl J Med 288: 1257-1261, Jun 14, 1973

10. LeBouvier GL: Subtypes of hepatitis B antigen. Clinical relevance? Ann Intern Med 79:894-896, Dec 1973

11. Hanshaw JB, Betts RF, Simon G, et al: Acquired cytomegalovirus infection: association with hepatomegaly and abnormal liver function tests. N Engl J Med 272:606-609, Mar 25, 1965

12. Reller LB, Barth 1: Granulomatous hepatitis associated with acute cytomegalovirus infection. Lancet 1:20-22, Jan 6, 1973

13. Penman HG: Fatal infectious mononucleosis—A critical review. J Clin Pathol 23:765-771, Dec 1970

14. Bar RS, DeLor JS, Clausen KP, et al: Fatal infectious mononucleosis in a family. N Engl J Med 290:363-367, Feb 14, 1974

15. Haller JS: The enigmatic encephalopathy of Reye's syndrome. Hospital Pract, pp 91-99, Feb 1975

16. Mirkovic RR, Adamov V, Boacher DW, Melnick JL: Identification of the "Kirk" hepatitis virus as a member of the parvovirus (picodna virus) group. Proc Soc Exp Biol Med 138:626-631, Nov 1971

17. Holmes AW, Wolfe L, Deinhardt F, et al: Transmission of human hepatitis to marmosets: Further coded studies. J Infect Dis 124:520-521, Nov 1971

18. Provost PJ, Ittensohn OL, Villarejos VM, et al: Etiologic relationship of marmoset-propagated CR 326 hepatitis A virus to hepatitis in man. Proc Soc Exp Biol Med 142:1257-1267, Apr 1973

19. Almeida JD, Rubenstein D, Stott EJ: New antigen-antibody system in Australia-antigen-positive hepatitis. Lancet 2:1225-1227, Dec 4, 1971

20. Jokelainen PT, Krohn K, Prince AM, et al: Electron microscopic observations on virus-like particles associated with SH antigen. J Virol 6:685-689, Jun 1970

21. Hirschman SZ, Vernace SJ, Schaffner F: DNA polymerase in preparations containing Australia antigen. Lancet 1:1099-1103, May 29, 1971

22. Kaplan PM, Greenman RL, Gerin JL, et al: DNA polymerase associated with human hepatitis B antigen. J Virol 12: 995-1005, Nov 1973

23. Brzosko WJ, Madalinski K, Krawczynski K, et al: Duality of hepatitis B antigen and its antibody—1. Immunofluorescence studies. J Infect Dis 127:424-428, Apr 1973

24. Brzosko WJ, Budkowska A, Slusarczyk J, et al: Varieties of HB Ag (Letter to the Editor). N Engl J Med 290:461-462, Feb 21, 1974

25. Hirschman SZ, Schwartz J, Vernace S, et al: An electron microscopic study of the structural polymorphism of hepatitis B antigen. J Infect Dis 128:605-617, Nov 5, 1973

26. Huang SN, Millman I, O'Connell A, et al: Virus-like particles in Australia antigen-associated hepatitis. Am J Pathol 67: 453-470, Jun 1972

27. Krugman S, Giles JP, Hammond J: Viral hepatitis type B (MS-2 strain)—Studies on active immunization. JAMA 217:41-45, Jul 5, 1971

28. Stephan W: Hepatitis-free and stable human serum for intravenous therapy. Vox Sang 20:442-457, May 1971

29. Holland P, Alter H, Purcell R, et al: Hepatitis-associated antigen and antibody in cold ethanol fractionates of human blood. Vox Sang 20:464-465, May 1971

30. Gerin JL, Purcell RH, Hoggan MD, et al: Biophysical properties of Australia antigen. J Virol 4:763-768, Nov 1969

31. Kim CY, Bissell DM: Stability of the lipid and protein of hepatitis-associated (Australia) antigen. J Infect Dis 123:470-476, May 1971

32. Kim CY, Tilles JG: Immunologic and electrophoretic heterogeneity of hepatitis-associated antigen. J Infect Dis 123:618-628, Jun 1971

33. LeBouvier GL: The heterogeneity of Australia antigen. J Infect Dis 123:671-675, Jun 1971·

34. Bancroft WH, Mundon FK, Russell PK: Detection of additional antigenic determinants of hepatitis B antigen. J Immunol 109:842-848, Oct 1972

35. Magnius LO, Espmark JA: New specificities of Australia antigen positive sera distinct from the LeBouvier determinants. J Immunol 109:1017-1021, Nov 1972

36. Barker LF, Peterson MR, Shulman NP, et al: Antibody responses in viral hepatitis, Type B. JAMA 223:1005-1008, Feb 26, 1973

37. Hoofnagle JH, Gerety RJ, Barker LF: Antibody to hepatitis-B virus core in man. Lancet 2:869-873, Oct 13, 1973

38. Desmet V: Chronic hepatitis (including primary biliary cirrhosis), chap 14, *In* Gall EA and Mostofi FK (Eds): The Liver. Williams and Wilkins, Baltimore, 1973, pp 286

39. Vital SBV, Thomas Jr W, Clowdus BJ: Acute viral hepatitis —Course and incidence of progression to chronic hepatitis. Am J Med 55:757-761, Dec 1973

40. Boyer JL, Klatskin G: Pattern of necrosis in acute viral hepatitis. N Engl J Med 283:1063-1072, Nov 1970

41. Davis MA, Peters RL, Redeker AG: Appraisal of the mortality in acute fulminant viral hepatitis. N Engl J Med 278:1248-1253, Jun 1968

42. Nielson JO, Dietrichson O, Elling P: Incidence and meaning of persistence of Australia antigen in patients with acute viral hepatitis—Development of chronic hepatitis. N Engl J Med 285: 1157-1160, Nov 1971

43. Goldsten GB, Lam KC, Mistilis SP: Drug-induced active chronic hepatitis. Am J Dig Dis 18:177-184, Mar 1973

44. Soloway RD, Summerskill WHJ, Baggenstoss AH: Clinical, biochemical, and histological remission of severe chronic active liver disease—A controlled study of treatments and early prognosis. Gastroenterology 63:820-833, Nov 1972

45. Alter HJ, Blumberg BS: Further studies on a "new" human isoprecipitin system (Australia antigen). Blood 27:297-309, Mar 1966

46. Prince AM: An antigen detected in the blood during the incubation period of serum hepatitis. Proc Nat Acad Sci 60:814-821, Apr 1968

47. Gocke DJ, Kavey NB: Hepatitis antigen—Correlation with disease and infectivity of blood donors. Lancet 1:1055-1059, May 31, 1969

48. Blumberg BS, Sutnick AI, London WT, et al: Medical intelligence. N Engl J Med 283:349-354, Aug 1970

49. Dawe DS, Cameron CH, Briggs M: Virus-like particles in the serum of patients with Australia-antigen-associated hepatitis. Lancet 1:695-698, 1970

50. Gerin JL, Holland PV, Purcell RH: Australia antigen: Large-scale purification from human serum and biochemical studies of its proteins. J Virol 7:569-576, May 1971

51. Le Bouvier GL: The heterogeneity of Australia antigen. J Infect Dis 123:671-675, Jun 1971

52. Le Bouvier G: Seroanalysis by immunodiffusion: the subtypes of type B hepatitis virus, chap 13, *In* Vyas GN, Perkins HA, Schmid R (Eds): Hepatitis and Blood Transfusion. New Haven, Conn, Grune & Stratton, 1972, pp 97-109

53. Feinman SV, Berris B, Sinclair JC, et al: Relation of hepatitis-B-antigen subtypes in symptom-free carriers to geographical origin and liver abnormalities. Lancet 2:867-869, Oct 20, 1973

54. Magnius L: Subtypes of hepatitis B antigen—Clinical relavance? (Personal communication). Ann Intern Med 79:894-896, Dec 1973

55. Magnius LO, Lindholm A, Lunden P, et al: A new antigen-antibody system—Clinical significance in long-term carriers of hepatitis B surface antigen. JAMA 231:356-359, Jan 1975

56. Walsh JH: Detection of virus antigens: Hepatitis B antigen. Metabolism 22:1111-1118, Aug 1973

57. Alter JH, Holland PV, Purcell RH: Counterelectrophoresis for detection of hepatitis-associated antigen—Methodology and comparison with gel diffusion and complement fixation, *In* Connor WE, Schedl JP (Eds): The Journal of Laboratory and Clinical Medicine. St. Louis, MO, the CV Mosby Company, 1971, pp 1000-1010

58. Purcell RH, Holland PV, Walsh JH, et al: A complement-fixation test for measuring Australia antigen and antibody. J Infect Dis 120:383-386, Sep 1969

59. Shaffer WE, Vyas GN, Shahed A, et al: Comparison of counterelectrophoresis and hemagglutination inhibition tests for hepatitis-associated antigen. Vox Sang 22:366-370, Oct 1971

60. Vyas GN, Shulman NR: Hemagglutination assay for antigen and antibody associated with viral hepatitis (Abstract), Science 170:332-333, Oct 1970

61. Barker LF, Shulman NR, Murray R, et al: Transmission of serum hepatitis. JAMA 211:1509-1512, Mar 1970

62. Walsh JH, Yalow R, Berson SA: Detection of Australia antigen and antibody by means of radioimmunoassay techniques. J Infect Dis 121:550-554, May 1970

63. Aach RD, Grisham JW, Parker CW: Detection of Australia antigen by radioimmunoassay. Proc Nat Acad Sci 68:1056-1060, May 1971

64. Hollinger FB, Vorndam V, Dreesman GR: Assay of Australia antigen and antibody employing double-antibody and solid-phase radioimmunoassay techniques and comparison with the passive hemagglutination methods. J of Immunol 107:1099-1111, Oct 1971

65. Lander JJ, Alter HJ, Purcell RH: Frequency of antibody to hepatitis-associated antigen as measured by a new radioimmunoassay technique. J of Immunol 106:1166-1171, May 1971

66. Ginsberg AL, Conrad ME, Bancroft WH, et al: Prevention of endemic HAA-positive hepatitis with gamma globulin—Use of a simple radioimmune assay to detect HAA. N Engl J Med 286: 562-566, Mar 1972

67. Overby LR, Decker RH, Ling CM: Nonspecificity of hepatitis B antigen detected with iodine-125-labeled antibody. Science 182:1368-1371, Dec 1973

68. Prince AM, Jass D, Brotman B: Specificity of the direct solid-phase radioimmunoassay for detection of hepatitis-B antigen. Lancet 1:1346-1350, Jun 1973

69. Alter HJ, Holland PV, Purcell RH: The ausria test: Critical evaluation of sensitivity and specificity. Blood 42:947-956, Dec 1973

70. Gocke DJ, Greenberg HB, Harvey NB: Correlation of Australia antigen with posttransfusion hepatitis. JAMA 212:877-879, May 1970

71. Goldfield M, Bill J, Black H, et al: Hepatitis associated with the transfusion of HB-Ag-negative blood, *In* Vyas GN, Perkins HA, Schmid R (Eds): Hepatitis and Blood Transfusion. New Haven, Conn, Grune & Stratton, 1972, pp 353-364

72. Walsh JH, Purcell RH, Morrow AG: Posttransfusion hepatitis after open-heart operations. JAMA 211:261-265, Jan 1970

73. Aach RD, Hollinger FB, Lander JJ, et al: Risk of transfusing blood containing antibody to hepatitis-B surface antigen. Lancet 2:190-193, Jul 1974

74. Purcell RH, Walsh JH, Holland PV, et al: Seroepidemiological studies of transfusion-associated hepatitis. J Infect Dis 123: 406-413, Apr 1971

75. Prince AM, Grady GF, Hazzi C, et al: Long-incubation posttransfusion hepatitis without serological evidence of exposure to hepatitis-B virus. Lancet 2:241-245, Aug 1974

76. Lander JJ, Giles JP, Purcell RH, et al: Viral hepatitis, type B (MS-2 strain): Detection of antibody after primary infection. N Engl J Med 285:303-307, Aug 1971

77. Holland PV, Walsh JH, Morrow AG, et al: Failure of Australia antibody to prevent post-transfusion hepatitis. Lancet 2:553-555, Sep 1969

78. Krugman S, Hoofnagle JH, Gerety RJ, et al: Viral hepatitis, type B, DNA polymerase and antibody to hepatitis B core antigen. N Engl J Med 290:1331-1335, Jun 1974

79. Hoofnagle JH, Gerety RJ, Ni LY, et al: Antibody to hepatitis B core antigen—A sensitive indication of hepatitis B virus replication. N Engl J Med 290:1336-1340, Jun 1974

80. London WT, Alter JH, Lander J, et al: Serial transmission in Rhesus monkeys of an agent related to hepatitis-associated antigen. J Infect Dis 125:382-389, Apr 1972

81. Krugman S, Giles JP, Hammond J: Viral hepatitis, type B (MS-2 strain): prevention with specific hepatitis B immune serum globulin. JAMA 218:1665-1670, Dec 1971

82. Prince AM, Szmuness W, Brotman B, et al: Hepatitis B immune globulin, *In* Vyas GN, Perkins HA, Schmid R (Eds): Hepatitis and Blood Transfusion. New Haven, Conn, Grune & Stratton, 1972, pp 335-347

Complications After Peptic Ulcer Surgery

The cardinal sign of malnutrition after surgical operation for peptic ulcer is weight loss. The cause of weight loss is not eating sufficiently. Although a few people have malabsorption after gastric operations, this is a relatively minor problem. The vast majority of people with weight loss after gastric operations do not eat enough—usually out of a fear of provoking post-cibal symptoms.

—JOHN ALEXANDER-WILLIAMS, MD, *England*
Extracted from *Audio-Digest Surgery,* Vol. 22, No. 4 in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Migraine—Medical Staff Conference, University of California, San Francisco. West J Med 123:211-217, Sep 1975

Medical Staff Conference

Migraine

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The first topic for presentation at Medical Grand Rounds today will be that of current concepts of migraine. We are very pleased to have Dr. Neil Raskin, Associate Professor of Neurology. Dr. Raskin will present a patient to us this morning and discuss this important topic.*

DR. RASKIN:† Thank you, Dr. Smith. Mr. S. has kindly consented to share his morning with us today. He has a rather interesting and unusual headache problem that I will have him tell you about. Although it is uncommon, it illustrates several pertinent points regarding the nature and mechanism of migrainous disorders. Mr. S. is now 64 years of age, and until five years ago only rarely experienced a mild headache. No one in his family has experienced headache, nor are there any circumstances that he can recall that have ever provoked headache.

Five years ago a cholecystectomy was carried out because of asymptomatic gallstones. After the patient ate his first postoperative meal, he experienced an extraordinary headache that persisted for about a day. Ever since then he has experienced headache upon the ingestion of certain foods; and I should like him to tell you about the foods that can do this and how soon after their ingestion he experiences headaches.

MR. S.: *It took quite a bit of analysis on my part to find out what foods actually did cause my headaches, and through elimination of certain foods from my diet, which took quite some time, I found that foods which contained a high degree of fat cooked at a high temperature or fried foods would induce a headache.*

DR. RASKIN: How long after eating these foods did you experience headache?

Patient: The headaches would start about an hour after eating fatty foods, and would last a minimum of 24 hours, depending on the amount of food.

DR. RASKIN: Other than fatty foods, there have been other foods that you discovered would cause headache; chocolate is one of them, is that correct?

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Neil H. Raskin, MD, Associate Professor of Neurology.

Patient: Chocolate used to cause headache, but I now take chocolate in moderation. Pressurized, oil-containing food, such as tuna or salmon, will give me a very severe headache. Soy sauce, frankfurters and bacon are also avoided.

DR. RASKIN: Did you ever go on a fruit diet to reduce your headache frequency?

Patient: Yes, it worked. However, while eating more fruits I would also watch my consumption of meats and how they were prepared.

DR. RASKIN: Where is your headache located?

Patient: The front bilaterally.

DR. RASKIN: Did your face ever discolor when you experienced headache, and is the nature of your headache ever pulsatile or is it a deep dull pain?

Patient: It is deep and dull, and with severe headaches the pain would seem to concentrate behind the eye: it felt in some cases like the eyeball was going to come out. My family tells me that my face is flushed when I have my headaches.

DR. RASKIN: Was it always the left eye or is it ever on the right side?

Patient: It is more concentrated on the left side.

DR. RASKIN: Do you ever see light flashes or sparkles or any other bright sensations with headache?

Patient: No.

DR. RASKIN: There have not been any other migrainous features to the patient's headache. Findings on skull and sinus x-ray studies were normal and several antihistamine preparations had been tried before my seeing him about a year ago. Upon the institution of ergonovine maleate, would you tell us what happened to your headache problem?

Patient: At first I took two tablets after each meal, morning, noon and night, and the headaches disappeared. Then gradually I reduced the number of tablets to two a day, two after the evening meal before I retired.

DR. RASKIN: Do you now have headache at all?

Patient: No, if I follow that procedure, no headaches.

DR. RASKIN: How many times during this past year have you gone off the pills?

Patient: A dozen or more for short durations.

TABLE 1.—*Foods Considered to be Migraine Precipitants and Excluded from the Diet of 240 Patients*

Food	*Number of Patients*	*Percent*
Chocolate	175	73
Dairy products (cheese)	114	48
Fruits (citrus)	80	30
Alcohol	60	25
Fatty fried food	45	19
Vegetables (onions)	42	18
Meat (pork)	35	15
Tea and coffee	35	15
Seafood	24	10

DR. RASKIN: What happened?

Patient: The headaches returned each time.

QUESTION: Does alcohol provoke his headaches?

Patient: No.

DR. RASKIN: Thank you very much, Mr. S., for spending this morning with us.

In summary, Mr. S., who is now 64, developed at the age of 60 a headache pattern that is rather nondescript; it is bifrontal and sometimes retroorbital in location, nonpulsatile and not associated with a characteristic aura. It was often severe pain. It appears to be controlled by the ingestion of an ergot alkaloid. Is this disorder migraine? I think so. Responsiveness to an ergot alkaloid is, in my view, the most useful definition of migraine presently available.

Mr. S.'s disorder is illustrative of the most interesting and exciting development in migraine research, something that has come to be known as "dietary migraine." Several years ago, a group in England headed by Edda Hanington[1] put together the data shown in Table 1 which were derived from a large number of patients with migraine. This is a group of food items that can provoke headache in certain susceptible patients who also have spontaneously occurring vascular headaches (migraine). Chocolate heads the list, followed by cheese, fruits, alcohol, fried foods and others. They compared this food group with another assortment of foods that were known to provoke headaches and hypertension in patients who had been taking monoamine oxidase (MAO) inhibitors. Cheese was the food most often incriminated, but other foods were implicated as well; the similarity between these two food groups is notable.

One of the offending chemical agents in these foods is tryamine, which liberates excessive norepinephrine from nerve endings if its degradative

pathway is blocked by an MAO inhibitor, producing acute elevations in blood pressure and headache. New York State cheddars are quite high in tyramine concentration, and chianti is higher than other wines (Table 2).[2] This correlates with some reports that chianti, more frequently than other red wine, triggers off headache in people so disposed. But you can even have your cheese and not have headache. The tyramine content of cheese is concentrated near the rind.[3] Cheese is abundant with tyrosine, which is decarboxylated to tyramine by decarboxylase-containing bacteria which are located in the rind. Therefore, if one were so inclined, one could slice away the rind and have one's cheese without eating much tyramine.

Since migraine is probably an hereditary disorder, there may be a genetic enzyme deficiency (possibly of monoamine oxidase) in some migraine sufferers. Such a deficiency might occasionally lead to increased tissue amine levels. A possible explanation of at least some attacks of migraine may be that in certain people there is a sensitive localized vascular response to circulating amines such as tyramine. To test this possibility, experiments were devised to ascertain whether migraine attacks could be precipitated by giving patients tyramine by mouth. It is now clear that patients with food-induced vascular headaches can be identified by their sensitivity to tyramine administration. In 17 patients with dietary migraine, headaches were produced 40 times in 49 administrations of tyramine, but only twice in 26 administrations of lactose tablets.[1] Patients with recurring headache disorders, but without food sensitivity, do not respond adversely to tyramine administration. There is clearly something different about patients with dietary migraine.

TABLE 2.—*Tyramine Content of Various Foods*

Product	*Tyramine (μg/g or μg/ml)**
Cheeses	
Camembert	86
Stilton	466
Brie	180
Emmentaler	225
New York State cheddar	1,416
Gruyere	516
Processed American	50
Cream	ND†
Cottage	ND
Yeast	ND
Yogurt	ND
Beer	
Brand A	1.8
Brand B	2.3
Brand C	4.4
Wine	
Sherry	3.6
Sauterne	0.4
Riesling	0.6
Chianti	25.4
Port	ND

*Cheeses expressed in μg/g; beers and wines in μg/ml.
†ND=not detected, being <0.2 μg/gm or μg/ml.

A problem with the tyramine hypothesis arose when it was learned that chocolate, which is at the head of this list of food offenders, contained no tyramine. However, it has recently been found that chocolate contains another vasoactive monoamine, phenylethylamine.[4] Patients who experienced headache after the ingestion of chocolate were challenged with phenylethylamine and headache was provoked much more frequently than after placebo administration. This took the monoamine oxidase theory up another notch. Since there is good evidence suggesting that monoamine oxidase exists in immunologically separable forms, for one of which phenylethylamine is the preferred substrate, a possible mechanism for chocolate-induced headache is that in these people there might be a deficiency of an isoenzyme of monoamine oxidase.

This possibility was examined by assessing platelet monoamine oxidase activity with various monoamine substrates in patients with migraine, in patients with chocolate-induced headache and in control subjects. The patients with chocolate-induced headache did not show a specific deficiency in phenylethylamine-dependent monoamine oxidase activity; the hypothesis is, therefore, not supported. On the other hand, in the patients with headache, both migraine and chocolate-sensitive, there was low platelet monoamine oxidase activity (compared with the control patients) which was statistically significant (Table 3). The activity was low with all four monoamine substrates used (phenylethylamine, tyramine, dopamine and 5-hydroxytryptamine).[4] This is one of the first biochemical distinctions ever made between patients with migraine and control subjects. They are preliminary data, but they provide an important clue toward understanding the migraine mechanism. This is the current status of the dietary migraine story; patients with food-precipitated headache comprise a rather small percentage of those patients with recurring headaches,

probably no greater than 5 percent. The other 95 percent of patients is the subject of the remainder of my remarks.

How can migraine be identified? Classical migraine is difficult to miss. We have all been taught to recognize hemicranial pulsating pain which is associated with retching and preceded by sparkling zigzags in a field of vision contralateral to the hemicephalgia. However, this classical syndrome is a rather uncommon one. It is certainly distinctive, but is representative of only a small fraction of the migraine population. The important public health problem, we all agree, is what has come to be called common migraine. Unfortunately, there is no consensus regarding the criteria or even the constituents of the latter disorder. Since this is a common source of discomfort for a large number of people, it is important to arrive at an operational definition of the disorder, since many effective pharmacological agents are now available for its treatment. By way of contrast, treatment nodes for muscle-contraction, or tension headache, are rather ineffectual in my experience; I avoid such a diagnosis until it becomes unreasonable to do so any longer. The large majority of patients with occipito-nuchal pain and muscle tightness also complain of headache, in another location, which usually bears the features of a vascular headache. At the head and neck, as in other parts of the body, muscle splinting in response to pain occurs. Recognizing the vascular component of these so-called mixed "tension-vascular" headaches will enable you to deal more effectively with your patients.

Let us consider the mechanisms underlying headache. Cerebral tissue is pain-insensitive; when pain is experienced about the head and neck vascular mechanisms are prominent: traction on the great venous sinuses or some of the large intracranial arteries, or dilatation of intracranial or extracranial arteries; in addition, inflammation of the meninges, or direct pressure upon the upper cervical roots are other important mechanisms. Many neurologists have come to the view that vascular mechanisms commonly underlie complaints of headache. Not all vascular headaches are migrainous; migraine is an idiopathic disorder, without underlying structural abnormalities. Lumbar puncture headaches are also vascular headaches. Headaches that occur in settings of vasculitis, as in periarteritis or lupus, are vascular headaches as well. These may be indistinguishable from what we might otherwise regard as migraine headaches. One of our jobs as physicians is to be sure that patients who present with vascular headaches, in fact, have no underlying structural cause for their complaint. In general, these causes are rather uncommon in dealing with patients with recurring episodic headaches. Harold Wolff provided the most direct evidence that the headache phase in migraine at least correlates with dilatation and stretching of arterial walls; nerve endings in these arterial walls relay this information centrally and pain is the response rendered. This is probably why the quality of pain experienced by the large majority of patients with migraine is a pulsatile, thumping or pounding sensation (throbbing).

The mechanism of the aura or of the migraine equivalents (migraine without headache) when they occur is probably through constriction of intracerebral arteries; the neurological symptoms that occur are dependent upon which part of the brain becomes ischemic. Aphasia, hemiplegia and tingling on one side of the body may occur; visual

TABLE 3.—*Human Platelet Monoamine Oxidase Activity*

Substrate	*Migraine*		*Patient Control*		*Chocolate-Sensitive Migraine*
Phenylethylamine	4.38±0.51 (28)	P<0.001	10.66±0.96 (26)	P<0.001	4.16±0.36 (12)
Tyramine	13.52±1.60 (28)	P<0.001	28.48±2.64 (26)	P<0.001	11.80±1.26 (12)
Dopamine	5.61±0.51 (28)	P<0.050	8.29±1.09 (26)	P<0.010	5.04±0.44 (12)
5-Hydroxytryptamine	14.54±1.17 (16)	P<0.010	21.70±1.82 (14)	P<0.050	15.84±1.88 (7)

P = statistically significant difference.

Each value is expressed as nanomole of substrate deaminated per 30 minute incubation per mg protein at 37°C. Protein nitrogen was measured according to the method of Lowry and co-workers[24] using human serum albumin as standard. Figures in parentheses represent number of subjects.

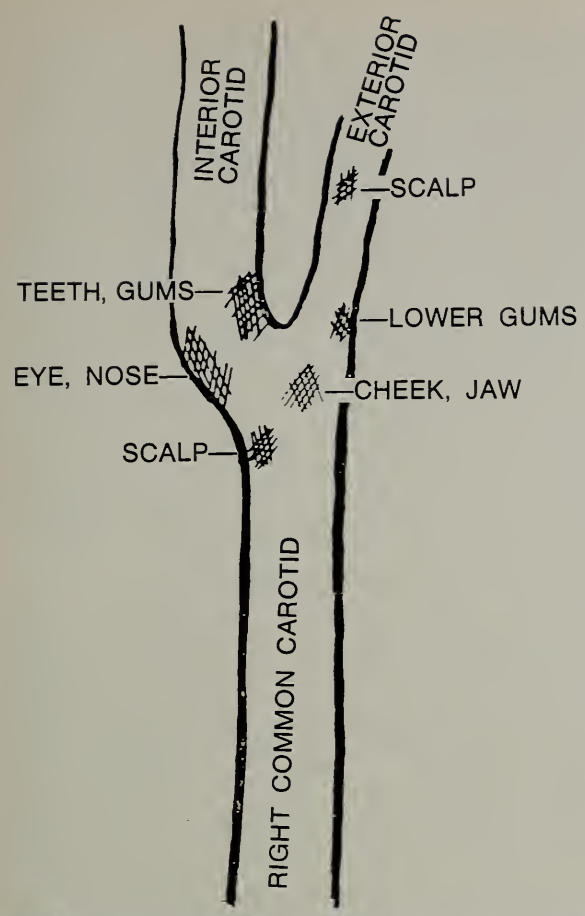


Figure 1.—Right common carotid artery and bifurcation with areas stimulated by faradic current showing reference of pain as determined by the patient during the period of stimulation. (Reproduced with permission from Ann Otol Rhinol Laryngol.[5])

symptoms are especially frequent because of the common involvement of the posterior cerebral artery in this process. Therefore, vascular headache disorders are comprised of both intracerebral vasoconstriction and extracerebral vasodilatation. Efforts at countering vasodilatation are useful therapeutically. Ice packs and the inhalation of 100 percent oxygen are helpful in general, whereas efforts that produce vasodilatation, such as heat applications or the ingestion of nitroglycerin tablets, may precipitate or exacerbate a vascular headache disorder.

It is perhaps intuitive that if one implanted electrodes in scalp arteries, pain would result in regions of the head overlying the vessel stimulated. It is not very well known that the carotid artery has special attributes. Fascinating experiments were done in the 1930's by Temple Fay[5] in Philadelphia, and reproduced by Bronson Ray in New York in the early 1940's, regarding the carotid artery wall and pain, which appear to corroborate a clinical observation that some of us have made recently. Electrodes implanted in the carotid artery near its bifurcation may produce pain over portions of the head and neck that I do not believe would have been predicted (Figure 1). Stimulation at one point produces pain in the cheek and jaw, a few millimeters away in the lower gums, another few millimeters laterally in the scalp, and so on. Carotidynia, or a painful carotid artery, is a term which has been rather vaguely used over the years. Dr. Stanley Prusiner and I have observed several patients in whom a tender carotid artery has been the apparent focus of a disorder characterized by episodic pulsatile neck or jaw pain in patients with preexisting migraine headaches.[6] This syndrome, carotidynia, has been responsive to administration of the very same drugs that alleviate migraine headaches. It is probably a migraine variant. We are now finding many patients with migraine in its many forms who have tender carotids, always ipsilateral to the episodic pain. Sometimes if the carotid artery is compressed, the patient's pain may be reproduced. This is a sign worth eliciting in a patient with a recurring pain disorder, and we believe it identifies its mechanism as migrainous.

The idea of central vasomotor instability, a putative mechanism underlying this group of disorders, is gaining support. The strongest evidence for vasomotor instability in patients with migraine stems from their responsiveness to a variety of biological stimuli. Exercise, an activity that is associated with vasodilatation of skeletal muscle arteries, sometimes causes headaches. Often these headaches are accompanied by scintillating scotomata ("sparkles"); thus, inappropriate cephalic vascular responses (vasomotor instability) to physical exertion occur in patients susceptible to migraine headaches and help us to recognize the migraine mechanism. There are other patients who, if they receive less than eight hours of sleep, awaken the next morning with headaches; others experience headache in association with menstruation, in response to flickering or bright lights, during the letdown period following stress or shortly after the drinking of an alcoholic beverage. These biological precipitants are probably more specific toward defining what migraine is than the descriptive features of classical migraine (aura, hemicranial headache, vomiting and the like). Headache that occurs an hour after only modest hunger and no clinically significant hypoglycemia is a common characteristic of migraine. People who, upon bending down for the soap in

the shower, arise quickly and experience a visual dim-out, scintillating scotomata or vertigo are more likely to experience migraine headaches.[7]

Let us return to other biological undercurrents of migraine. In the late 1950's, methysergide was brought forth for migraine prophylaxis. This agent was and is used daily to block the migraine mechanism, thus preventing headache occurrences. During the early clinical trials, it was clear that it was, indeed, effective but to the surprise of most it was found not to be a potent vasoconstrictor; in fact, there was a poor correlation between headache relief and evidence of vasoconstriction. The mechanism of action of methysergide was an open question. It was then learned that methysergide was a pharmacological antagonist of serotonin, which set off a wave of speculation that serotoninemia characterized the migraine state.[8] Against this notion was the observation that headache is not a feature of the carcinoid syndrome; furthermore, infusions of serotonin in patients with migraine alleviated their headache, presumably because of the vasoconstrictor effect of serotonin. However, urinary metabolites of serotonin were measured, and it was found that there was an excess of 5-hydroxyindoleacetic acid during the headache phase of migraine. Lance has shown that there is a 30 percent decrease in platelet serotonin during a migraine headache.[9] This is a finding that has now been reproduced by several laboratories and appears to be a consistent biological concomitant of migraine. However, further interactions of serotonin with the organism are not at all clear. No serotonin appears in cerebrospinal fluid, for example, during headache. The initial enthusiasm regarding the implication of serotonin in migraine has not met with the reward of insight. On the other hand, it has led to a group of drugs, some of which are thought to be serotonin antagonists, which are generally effective in ameliorating the migraine state.[10] Thus, it has been operationally useful to pursue the hypothesis that serotonin is somehow involved in the migraine mechanism.

TABLE 4.—*Differences Between Migraine and "Migrainous Neuralgia"*

	Migraine	*"Migrainous Neuralgia" (cluster headache)*
Frequency of attacks	<1-12/month	1-8/day
Usual duration of pain	4-24 hours	0.25-2 hours
Sex incidence	female 75%	male 85%
Onset in childhood	25	<1
Unilateral pain	65	100
Recurrence in bouts	0	80
Associated features:		
nausea, vomiting	85	45
blurring of vision	common	8
lacrimation	uncommon	85
blocked nostril	uncommon	50
ptosis, miosis	uncommon	25
hyperalgesia of face, scalp	65	15
teichopsia, photopsia	40	<1
polyuria	30	7
Past health:		
vomiting in childhood	25	7
Family history:		
migraine	50	20
Biochemical changes:		
fall in plasma serotonin	80	0

There is even an experimental model of migraine. After the subcutaneous injection of rather large amounts (2.5 mg) of reserpine, a vascular headache appears in four to six hours in patients who have spontaneous migraine headaches.[11] The platelet serotonin also drops in response to reserpine. This response of serotonin to reserpine also occurs in nonmigrainous patients and they do not experience headache after the injection of reserpine. Furthermore, a reserpine-induced headache can be blocked with methysergide, but the decrease in platelet serotonin in unaffected. It is not at all clear what the decrease in serotonin has to do with the fundamental mechanism of headache; it may be an epiphenomenon. Of course, what happens in the central nervous system need not be reflected by changes in peripheral blood; serotonin-related metabolic events in neurons is perhaps more important than what is happening in platelets. Inasmuch as there is no animal model of migraine, this is impossible to test in our current state of knowledge.

There are other drugs which have been shown to be useful in the prophylaxis of migraine for which there is little or no evidence of serotonin antagonism or of vasoconstriction—propranolol,[12] clonidine,[13] tricyclics.[14] My own working hypothesis is that they depress central vasomotor instability; there are very few data that bear on this, however.

I want to turn now to another variant of migraine. It is useful to regard this disorder as migraine because it is responsive to the same group of pharmacological agents. In all other ways it is different. It has many names: migrainous neuralgia, cluster headache, red migraine, Horton's

histaminic cephalgia, Sluder's neuralgia and others.[15] The mechanism of this disorder probably involves intracranial arterial vasodilatation. It occurs predominantly in men, whereas migraine most often occurs in women (Table 4). It starts in the fourth and fifth decade, whereas migraine begins in childhood through the third decade. Cluster headaches characteristically waken people from sleep. They are associated with eye pain that is generally nonpulsatile in quality and are not usually associated with scintillating scotomata or vomiting. Often they are associated with tearing and reddening of the eye, puffiness of the periorbital tissue, stuffiness of the nose ipsilaterally and as the pain wears off in 10 to 20 minutes—these are short bursts of pain—the nose begins to run. All of these occur on the same side as the pain. The attacks occur one to several times per day for several weeks, stop for a while, and then recur. This cluster tempo is distinctive. There is no diminution of platelet serotonin in this condition; nor does there tend to be a high familial prevalence of the condition, as there does in migraine. These disorders are quite different genetically, clinically and biochemically. Yet the same group of drugs is effective for all of these patients.

What we have called migraine today is strictly an operational gesture. Your patients will benefit from your recognition of this common problem. In the not too distant future, several different disorders with distinctive mechanisms will probably emerge from this patient population. Until then, let us all keep our minds open regarding the nature of this disorder. We have certainly come a long way from the notion that migraine is primarily a psychosomatic disorder, a prevalent view 20 years ago.

REFERENCES

1. Hanington E, Harber AM: The role of tyramine in the aetiology of migraine, and related studies on the cerebral and extracerebral circulations. Headache 8:84-97, Oct 1968
2. Horwitz D, Lovenberg W, Engelman K, et al: Monoamine oxidase inhibitors, tyramine, and cheese. JAMA 188:1108-1110, Jun 29, 1964
3. Price K, Smith SE: Cheese reaction and tyramine. Lancet 1:130-131, Jan 16, 1971
4. Sandler M, Youdim MB, Hanington E: A phenylethylamine oxidising defect in migraine. Nature 250:335-337, Jul 1974
5. Fay T: Atypical facial neuralgia, a syndrome of vascular pain. Ann Otol Rhinol Laryngol 41:1030-1062, Mar 1932
6. Prusiner SB, Raskin NH: Carotodynia—A remediable vascular pain in the neck. Neurology 23:398, Apr 1973
7. Raskin NH, Knittle SC: Migraine: thermal and orthostatic phenomena. Neurology 25:379-380, Apr 1975
8. Dalessio D: On migraine headache: serotonin and serotonin antagonism. JAMA 181:318-321, Jul 28, 1962
9. Anthony M, Hinterberger H, Lance JW: Plasma serotonin in migraine and stress. Arch Neurol (Chicago) 16:544-552, May 1967
10. Lance JW: The Mechanism and Management of Headache. London, Butterworths, second edition, 1973, 205 pp
11. Tandon RN, Sur BK, Nath K: Effect of reserpine injections in migrainous and normal control subjects, with estimations of urinary 5-hydroxyindoleacetic acid. Neurology 19:1073-1079, Nov 1969
12. Wideroe TE, Vigander T: Propranolol in the treatment of migraine. Br Med J 2:699-701, Jun 1974
13. Shafer J, Tallett ER, Knowlson PA: Evaluation of clonidine in prophylaxis of migraine. Double-blind trial and follow-up. Lancet 1:403-407, Feb 19, 1972
14. Gomersall JD, Stuart A: Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 36:684-690, Aug 1973
15. Lance JW, Anthony M: Migrainous neuralgia or cluster headache? J Neurol Sci 13:401-414, Aug 1971

Presence of Abscess

In general, the problem of pus for the surgeon is the problem of diagnosing the cause of unexplained fever. After we have gone through the regular ritual of looking at the urine, looking at the lungs, looking at the wound and looking for phlebitis, one of the common causes of fever today, we are ready to consider abdominal abscess. I make it a cardinal point in my practice never to explore the abdomen or the chest looking for an abscess that I have not already found with a needle or by palpation, feeling a mass in the abdomen. I never explore for an abscess. I have got to find it. And the way to find it is by repeated, careful, deliberate, systematic physical examination by the same observer several times a day, every day. It is the fever that is the tipoff to the presence of the abscess. The leukocyte count helps me not at all.

—MARK M. RAVITCH, MD, *Pittsburgh*

Extracted form *Audio-Digest Surgery*, Vol. 22, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057

Important Advances in Clinical Medicine

Epitomes of Progress—Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Medical Aspects of Noise

WORLDWIDE INTEREST in combating pollution has led to questions regarding the effects on man of various noxious agents. Air pollution is mentioned more frequently in the press, but noise pollution results in more complaints from the populace. These complaints appear to be well founded since recent studies indicate that the effects of noise may be worse than suspected.

The auditory effects of noise have been studied extensively and are well documented. The nonauditory effects of noise (annoyance; interference with sleep, speech, or work performance; psychological effects, and physiological effects) are now receiving more attention. Davis, Rosen, Jansen and others have previously shown that there is a relationship between noise exposure and the cardiovascular system. There is some evidence that prolonged exposure to excessive noise can result in peripheral circulatory disturbances and heart disease. Recent studies indicate that body chemistry changes occur during prolonged exposure to noise. Specifically, cholesterol and cortisol rise during noise exposure and decrease during quiet.

The general population seems to be alarmed about the rising noise levels and public pressure has resulted in federal, state and local regulations concerning maximum allowable noise levels and exposures. It is important for physicians, particularly otolaryngologists, to be aware of the effects of noise and pursue further studies to determine the extent of the nonauditory effects of noise.

ROBERT W. CANTRELL, MD

REFERENCES

Kryter KD: The Effects of Noise on Man. New York-London, Academic Press, 1970

Miller JD: Effects of noise on people. J Acoust Soc Am 56:729-764, Sep 1974

Cantrell RW: Prolonged exposure to intermittent noise—Audiometric, biochemical, motor, psychological and sleep effects. Laryngoscope Supp 1, 84:1-55, Oct 1974

Hearing Aids for Unilateral Hearing Loss

PATIENTS WHO ARE DEAF in one ear, with normal hearing in the other ear, have considerable difficulty understanding in certain situations. Problems arise when these persons try to carry on a conversation in groups of people; when someone is seated on the side of their impaired ear, or when they are in a theater, meetings or conferences.

The use of a CROS-type (contra-routing of signal) hearing aid can be helpful in some of these situations. The CROS aid is available in either eyeglasses or in behind-the-ear instruments. The microphone is placed on the ear with impaired hearing and the sound is routed into the better hearing ear. An open-type earmold is used.

Purchase of a CROS aid should always be on a rental-trial basis. A thirty-day trial period enables a patient to evaluate the effectiveness of the aid and his tolerance for CROS amplification.

E. W. JOHNSON, PH D

REFERENCES

Harford E, Dodds E: Versions of the CROS hearing aid. Arch Otolaryngol 100:50-57, Jul 1974

Johnson EW: CROS—Bi-CROS Amplification. Presented at the 1974 Oticongress, Feb 1974, Copenhagen, Denmark

Mandibular and Maxillary Osteotomy

ESTHETIC SURGEONS over the years have used rhinoplasty as the principal procedure in improving the appearance of patients with facial disharmony. More recently, the combination of a recessive chin and a large nose has been treated by the combination of rhinoplasty and chin-augmentation, using for the latter either the excised nasal hump or a preformed alloplastic implant. Until the pioneering work of Obergaser and Tessier, a patient with severe facial disharmony was beyond surgical redemption.

These patients usually present with the following problems: protrusive or prognathic mandible, recessive or retrognathic mandible, small chin or microgenia, recessive maxilla, protrusive maxilla and hypertelorism. These problems can vary in severity from a patient with a retrognathic mandible and a class II malocclusion to the horribly disfiguring countenance of a patient with Crouzon's disease.

Although the deformities in most of these persons are inherited and resemble these characteristics in their parents, many occur secondary to disease states.

Evaluation of these patients includes a careful examination of the nose, throat, teeth and facial bones. A meticulous analysis of the occlusal relationships of the teeth is essential. The occlusion and cephalometric radiographs should be examined in conjunction with an orthodontist. The construction of a cast of the patient's teeth in dental stone and setting them up in an articulator is a vital step in the assessment of the deformity and the planning of reconstruction.

Retrognathia may be corrected using a horizontal osteotomy of the mandibular parasymphyseal and anterior body regions then sliding this segment forward and fixing it in place with a figure-of-eight wire. Prognathism is effectively treated using a sagittal osteotomy of the mandibular rami placed obliquely from medial to lateral extending from above the cingulum, guarding the inferior alveolar nerve, to the lower lateral border of the angle of the mandible taking care to avoid the nerve. The anterior segment is slid backward and the teeth are fixed in their new occlusal relationship using arch bars and intermaxillary wires.

Maxillary retrusion and protrusion are treated by creating LeFort fractures and repositioning of the maxillae in the desired position, fixing them in place with interosseus wires in similar fashion to repairing a facial fracture. The teeth are wired into occlusion. A pronounced overbite and overjet that is not amenable to orthodontic therapy can be notably improved by extraction of a premolar tooth on each side of the maxilla, the excision of a strip of palatal bone, an horizontal osteotomy of the anterior palate and a pushing back and wiring of the segment. Pronounced stenosis of the maxilla as seen as a residuum following repair of a severe bilateral cleft palate deformity must be corrected by a LeFort II fracture and sometimes the insertion of bone grafts to maintain position.

The most severe cases of facial disharmony are seen in cranio-facial dysostosis such as in Crouzon's disease and Apert's syndrome. Their correction requires a combined neurosurgical approach through a large frontal bone flap to expose the orbital roofs, then the construction of a LeFort III fracture by the facial plastic surgeon. Removal of a central wedge of bone is done to

correct the hypertelorism, and enlargement of the orbits in those cases with exorbita is necessary to accommodate the extruded globes. The latter is a prodigious surgical procedure to be undertaken only by those with a great deal of experience in maxillofacial surgical procedures.

The surgical correction of facial deformities by repositioning of the jaws is a gratifying procedure usually yielding a pronounced improvement in facial harmony.

PAUL J. DONALD, MD

REFERENCES

Hinds EC, Kent JN: Surgical Treatment of Developmental Jaw Deformities. St. Louis, C. V. Mosby Company, 1972

Gable WC, Rosenstein SW, Bzoch KR: Cleft Lip and Palate —Surgical Dental and Speech Aspects. Boston, Little, Brown and Company, 1971, pp 499-582

Advances in Endoscopy of the Respiratory and Upper Digestive Tract

EXAMINATION OF THE upper respiratory and upper digestive tract has undergone gradual refinements during the past century. The use of reflected proximal lighting of the endoscopes has been replaced with distal lighting in the various endoscopes.

The application to endoscopy of two new major optic and engineering developments has completely revolutionized the quality and extent of the information that can be obtained. The development of coherent flexible fibroptic endoscopes has facilitated rapid examination of the tracheobronchial tree and esophagus under local anesthesia. It has proven particularly successful in the bedside examination of lesions in the esophagus and stomach and has expanded the visualization of the next order peripheral segmental branches of the tracheobronchial tree. There are many limitations of the technique and it is not without hazard.

Simultaneously a new Hopkins rod optical system has completely revolutionized the construction of endoscopic telescopes to open tube endoscopy. In the new Hopkins rod lens system the air interspaces between the bi-convex glass lenses have been replaced with glass rods with polished ends separated by small air lenses. The improved optics and magnification produced by this new invention allow incorporation of a surrounding fibroptic light bundle which provides better visualization and image resolution, and provides adequate light for photography. The merits of permanent documentation by photography are obvious. An endoscopist who incorporates these new instruments into his endoscopic armamentarium will find they help him achieve superior quality of examination.

The Hopkins rod lens system has also been incorporated into a wide angle side view telescope that allows excellent indirect examination of the larynx, pharynx and nasopharynx. This new instrument will enable a family physician or any other doctor to examine these areas with much greater facility than previously possible with a head mirror and nasopharyngeal and laryngeal mirrors.

It is hoped that the ability to visualize these areas by almost all physicians will lead to earlier diagnosis of diseases of the nasopharynx, pharynx and larynx.

PAUL H. WARD, MD

REFERENCES

Berci G, Ward PH, Besci G, et al: Advances in endoscopic examination of the respiratory system. Presented at the 54th Annual Meeting of the American Broncho-Esophogal Assn, Apr 25, 1974 Palm Beach. Ann Oto Rhinol Laryngol 83:754, Nov-Dec, 1974

Ward PH, Berci G, Calcatera TC: Advances in endoscopic techniques for examination of the larynx and naso-pharynx. Presented to the Centennial Conference on Laryngeal Cancer, May 28, 1974, Toronto. Laryngoscope 84:2181-2194, Dec. 1974

Hair Transplant

THE HAIR transplant autograft continues to be a useful and reliable technique for a surgeon interested in head and neck reconstructive and cosmetic surgical procedures. Emphasis has been on restorations of male pattern hair loss. However, the operation also is useful in restoring hair lost by trauma or surgical scars. We have used the hair transplant successfully in the scars of a temporal face-life, and have grafted a moustache into the scar of a cleft-lip repair. Even thin atrophic scars can be grafted slowly in multiple stages.

Hair survival in the grafts should be at least 90 percent when attention is paid to careful technique. Failure of such hair to grow is often due to poor graft preparation or to insufficient circula-

tion in the recipient area. Training seminars, films, videotapes, micro-films and texts are now available to illustrate the various techniques. The first Hair Transplant Symposium and Workshop was held in Arkansas in 1974, sponsored by the Society for Dermatologic Surgery and the American Academy of Facial Plastic and Reconstructive Surgery.

Briefly noted, success requires: (1) atraumatic preparation of the grafts using *sharp* cutters, either power driven or hand held; (2) preservation of the grafts in cold saline; (3) placement of the grafts with attention to the availability of circulation and to aesthetic considerations.

CHARLES M. MONELL, MD

REFERENCES

Monell C: The success or failure of the hair transplant. Arch Otolaryngol 97:265-268, Mar 1973

Monell C: Hair transplant—A variation of the Orentreich technique. (Syllabus) Aesthetic Reconstr Facial Plast Surg (Microfilm), Feb 19, 1974

ADVISORY PANEL TO THE SECTION ON OTOLARYNGOLOGY

HERBERT DEDO, MD, *Chairman, San Francisco*
University of California, San Francisco

MANSFIELD SMITH, MD
CMA Section on Otolaryngology
Chairman
San Jose

ROBERT KOHUT, MD
CMA Section on Otolaryngology
Secretary
University of California, Irvine
California College of Medicine

ROGER BOLES, MD
CMA Section on Otolaryngology
Assistant Secretary
University of California, San Francisco

HOWARD HOUSE, MD
CMA Scientific Board
Los Angeles

ROBERT ROWE, MD
Loma Linda University

F. BLAIR SIMMONS, MD
Stanford University

LESLIE BERNSTEIN, MD
University of California, Davis

PAUL DONALD, MD
University of California, Davis

PAUL WARD, MD
University of California, Los Angeles

ALAN NAHUM, MD
University of California, San Diego

ALDEN MILLER, MD
University of Southern California
Los Angeles

DALE TIPTON, MD
San Francisco

MAURICE SCHIFF, MD
La Jolla

EDITORIALS

The Third Segment of Medical Education

MEDICAL EDUCATION has traditionally been more or less divided into two segments. Undergraduate education, the training of medical students, is the oldest. Then the formal training of interns, residents and fellows was added and has become a recognized second segment. Although it is well known and often preached that medical education for practicing physicians is a lifetime affair, this third segment of medical education has so far received considerably less attention and consequently is much less developed.

Continuing education, as this third segment is commonly called, is now starting to come into its own. This is because scientific medicine and the so-called half-life of medical knowledge are advancing so rapidly that the experience every physician accumulates in practice and the knowledge gained from contact and discussion with colleagues is no longer enough to satisfy the physician himself, his patients or the public that he is indeed keeping abreast of all the new and useful things that can be brought to bear in patient care. So continuing education is in the process of becoming more formalized as it receives increasing attention from both the profession and the public. But there is quite a way to go before it is fully recognized as the third segment of medical education.

The three segments are distinct yet they form a continuum. They are distinct in the degree of patient care responsibility to be found in each. In undergraduate training there is little or no direct responsibility for patient care and the aim is to acquire the basic knowledge and skills to provide a framework for future learning. In postdoctoral training there is graduated but supervised responsibility for patient care and the aim is for the young physician to gain the knowledge, skills and experience to assume full responsibility for primary or specialty care in the field of his choice. In continuing education the aim is to assure that new knowledge from the laboratory and elsewhere is continually added to the knowledge a physician accumulates from his practice experience so that his care of patients remains up to date and of high quality.

It is suggested that continuing medical education should become fully recognized as a genuine third segment of medical education. If this is to occur there is need to come to grips with such things as what should be taught, by whom, to whom and by what means, and how this educational effort is to be linked to the actual and perceived needs of the physician and the needs of his patients in his own practice situation. It may well be that the part played by medical schools and academic medicine should be substantially strengthened, particularly with respect to what should be taught, what is new and sufficiently proved to be added, and what has become obsolete and should no longer be used in practice. So far the role of the medical schools has been quite minor compared with the overall activities of medical associations, specialty societies, voluntary health agencies, pharmaceutical firms, travel agencies and others in both the public and private sectors.

Perhaps the fourth Planning and Goals Conference soon to be held by the California Medical Association will shed some much needed light on this whole very important subject.

—MSMW

Man, Mice and Glycogen Storage

In light of the abnormalities in glycogen metabolism in man, Gross reviews in this issue two situations in mice where genetic abnormalities in the enzymes of glycogen metabolism are present.

In one of these conditions, the radiation-induced glucose-6-phosphatase deficiency in mice, the condition has not yet shed light on the human genetic disease. These mice actually have very low liver glycogen concentrations and die of hypoglycemia in the immediate newborn period. They might be valuable models if in the future they could be supported during the newborn period (possibly with parenteral nutrition) so that they may adapt to their absence of glucose-6-phosphatase activity as do humans. Such efforts to adapt these mice and have them survive would indeed be of interest and possibly create very valuable models for experimentation.

The mice with the genetic deficiency of phosphorylase-b-kinase have been considerably more informative. The dramatic lack of enzyme activity in these mice (and indeed their ability to exercise more strenuously than controls) is striking. The mechanism of their glycogenolysis has been extensively studied in a fashion that in man would be most difficult.

Gross outlines four principles to be drawn from mice and applied to the human glycogenoses. Certainly age-matched control specimens from muscle biopsies in all situations are most desirable. A whole host of conditions other than primary genetic enzyme deficiencies can reduce enzyme activity in muscle biopsy specimens in man, such as inflammatory disease and degenerative neurologic disease. Operationally, however, genetic deficiencies of enzymes in humans should only be seriously considered when there is essentially a total absence of activity. The absence, therefore, of an accurately matched specimen should not dramatically impair clinical diagnosis.

Fortunately, fewer reports are appearing in the literature of multiple enzyme deficiencies in the glycogen storage diseases in man. Most of the reported instances in these situations are clear-cut laboratory errors arising most likely from problems in handling tissues. If one looks carefully at the reported multiple enzyme deficiencies in man, there is a striking relationship between the lability of the enzyme and the frequency with which it is reported as being involved in a combined deficiency. However, it has been our feeling that glucose-6-phosphatase activity is depressed fairly consistently in patients with debrancher deficiency glycogen storage disease, sometimes quite notably. An analysis of our own data on freshly obtained biopsy specimens from five recent patients with debrancher deficiency supports this impression. It is surprising to me, with the pronounced abnormalities in hepatic architecture and the pronounced hormonal changes in blood, that even more dramatic secondary changes do not occur.

It is not surprising that Gross, on a careful examination of the b-kinase activity in his mouse extracts, was able to show the presence of a cross-reacting protein. It has become the usual story in human biochemical genetics when a critical study is made of residual activity or for the presence of an altered protein in the absence of enzyme activity, an altered enzyme protein is usually found. Even in the long-considered best candidate for a regulatory mutation in man (hereditary orotic aciduria), recent studies have shown the presence of structurally abnormal enzyme protein.

It seems clear to me that the findings from studies made on phosphorylase-b-kinase deficient mice can, because of the availability of the tissue with unlimited experimental conditions, be used and can shed a great deal of light on the mechanism of phosphorylase activation and what might be anticipated in some b-kinase-deficient patients.

The glycogen body, an interesting structure that normally is present at the base of the spinal cord of birds, has recently been the subject of fairly extensive study. This structure, collar button in size, contains an enormous amount of structurally normal glycogen. This glycogen turns over and appears to have phosphorylase that is similar to liver phosphorylase. This structure lacks glucose-6-phosphatase activity but has all the other enzymes involved in glycogen synthesis and degradation. In a sense, therefore, it could be used as a model under some circumstances for glucose-6-phosphatase deficiency.

Findings from studies of human glucose-6-phosphatase deficiency have shown increasing numbers of abnormalities in circulating hormones, which are known to affect the activities of liver

enzymes involved in glycogen metabolism. The ability to correct the hormonal abnormalities (as well as the clotting abnormalities, and the lipid and uric acid abnormalities) by total parenteral nutrition should offer a unique opportunity to see which of the effects of the hepatic glucose-6-phosphatase deficiency are related directly to the genetic defect, per se, and which are due to the secondary hormonal abnormalities.

R. Rodney Howell, MD
Professor and Chairman
Department of Pediatrics
University of Texas Health Science Center
Houston

Promising Developments in Viral Hepatitis

The specialty conference on viral hepatitis in this issue of the Journal is timely because of the many recent advances that have created optimism for the early unraveling of the virology of these diseases. Some of the important developments deserve further emphasis.

Perhaps the most welcome recent advance was the development of a specific complement-fixation test[1] and a specific immune adherence test[2] for the identification of hepatitis A virus (HAV) antibody by Hilleman and his associates. These tests for the detection of hepatitis A antibody were made possible by the isolation of the CR 326 strain of human HAV in marmosets (Saguinus mystax) and the use of antigen prepared from livers of infected marmosets.[3,4] CR 326 was isolated in Costa Rica from the blood of a child with typical clinical infectious hepatitis by serial passage in marmosets.[3] Neutralizing antibody to CR 326 developed in patients with hepatitis A infection; no such antibody was detected in patients with hepatitis B infection.[4] These studies bring to practical fruition work began by Deinhardt and co-workers[5] in the mid-1960's when this group reported the transmission of human viral hepatitis to marmoset monkeys. Although results of further investigation showed that the virus (G.B. agent) was not true human HAV, these workers subsequently were successful in transmitting the MS-1 strain of HAV to marmosets.[6] A recent study by Krugman and co-workers[7] has confirmed the specificities of the complement-fixation and immune adherence tests for HAV. The immune adherence test seemed to be more specific, more sensitive and simpler to carry out than the complement-fixation test. Anti-HAV antibody was detected by the immune adherence test within one to four weeks after onset of hepatitis. In 80 percent of patients the antibody was detected within the first two weeks after the onset of clinical hepatitis. These tests for anti-HAV are easier to do than the immune electron microscopy test for anti-HAV introduced by Feinstone and associates,[8] and have the important advantage of quantitation. The availability of specific, easily carried out tests for HAV now open the way to extensive epidemiologic studies of this viral infection. Much more should be learned about the sequelae of HAV infection in man. Furthermore, the marmoset appears to offer an animal model, albeit a rather expensive one, for the laboratory study of the biology of the virus. Although Hilleman's group[9] has suggested that HAV is an enterovirus-type particle, containing ribonucleic acid (RNA), very little is known at present of the biochemistry of this virus.

There has been some headway in the elucidation of the nature of the hepatitis B virus (HBV). Deoxyribonucleic acid (DNA) has been isolated from HBV cores purified from the nuclei of infected human liver,[10] and from cores of serum Dane particles.[11] Thus HBV appears to be a unique small DNA-containing virus carrying its own DNA polymerase. The DNA polymerase[12] associated with the Dane particle[13] has become the biochemical tag of the putative HBV and also affords a probe for the study of the synthesis of the virus in infected human liver through the use of radiolabeled viral DNA synthesized in test tubes. It should be noted that although the Dane particle is the most likely candidate for the infectious HBV particle there is as yet no hard evidence to prove this assumption.

The suggestion by Dane and his colleagues[14] that particulate hepatitis B surface antigen (HBs Ag) found in the sera of patients with hepatitis B infection, was the excess coat protein of HBV perforce led to the conclusion that HBs Ag was not infectious. The separation of hepatitis B core antigen (HBc Ag) from HBs Ag in the Dane particle by Almeida and co-workers[15] reinforced this conclusion. This imediately raised the possibility that, although HBs Ag was not infectious, antibody to the antigen might be protective. Indeed, Krugman and associates[16] had already shown that immuni-

zation with a boiled preparation of MS-2 serum provided resistance to subsequent infection with the MS-2 strain of HBV. Pilot studies by Purcell and his co-workers (personal communication) in several chimpanzees have shown that purified preparations of HBs Ag, although not infectious, do provide protection against subsequent inoculation with infectious serum. However, I would echo the call for caution raised by Zuckerman[17] concerning the use of such vaccines in humans before extensive testing in animals.

Although the recent advances in viral hepatitis are heartening, they also bring into sharper focus a new problem. The new tests for HAV, combined now with various tests for detection of HBV infection, have afforded substantiation of the claims that a high proportion of transfusion-association hepatitis is caused by as yet unidentified infectious agents, neither HAV nor HBV.[18,19] Feinstone and co-workers[20] recently studied 22 patients each of whom had an episode of transfusion-associated hepatitis negative for HBs Ag, HBc Ag and the respective antibodies to these antigens. Antibody response to HAV was measured by immune electron microscopy. None of the 22 patients developed serologic evidence of HAV infection. Whether such unidentified infectious agents are also important causes of hepatitis in human populations at large will require much study. Nevertheless, it is evident that the more is learned about viral hepatitis the more appears to remain unknown.

SHALOM Z. HIRSCHMAN, MD
Professor of Medicine
Director, Division of Infectious Diseases
Mount Sinai School of Medicine
of the City University of New York

REFERENCES

1. Provost PJ, Ittensohn OL, Villarejos VM, et al: A specific complement-fixation test for human hepatitis A employing CR326 virus antigen: Diagnosis and epidemiology. Proc Soc Exp Biol Med 148:961-968, Apr 1975

2. Miller WJ, Provost PJ, McAleer WJ, et al: Specific immune adherence assay for human hepatitis A antibody: Application to diagnostic and epidemiologic investigations. Proc Soc Exp Biol Med 149:254-261, May 1975

3. Mascoli CC, Ittensohn OL, Villarejos VM, et al: Recovery of hepatitis agent in the marmoset from human cases occurring in Costa Rica. Proc Soc Exp Biol Med 142:276-282, Jan 1973

4. Provost PJ, Ittensohn OL, Villarejos VM, et al: Etiologic relationship of marmoset-propagated CR326 hepatitis A virus to hepatitis in man. Proc Soc Exp Biol Med 142:1257-1267, Apr 1973

5. Dienhardt F, Holmes AW, Capps RB, et al: Studies on the transmission of human viral hepatitis to marmoset monkeys—I. Transmission of disease, serial passages, and description of liver lesions. J Exp Med 125:673-689, Apr 1, 1967

6. Holmes AW, Wolfe L, Rosenblate H, et al: Hepatitis in marmosets: induction of disease with coded specimens from a human volunteer study. Science 165:816-819, Aug 22, 1969

7. Krugman S, Friedman H, Lattimer C: Viral hepatitis, type A—Identification by specific complement fixation and immune adherence tests. N Engl J Med 292:1141-1143, May 29, 1975

8. Feinstone SM, Kapikian AZ, Purcell RH: Hepatitis A: Detection by immune electron microscopy of a virus-like antigen associated with acute illness. Science 182:1026-1028, Dec 7, 1973

9. Provost PJ, Wolanski BS, Miller WJ, et al: Physical, chemical and morphologic dimensions of human hepatitis A virus strain. Proc Soc Exp Biol Med 148:532-539, Jan 1975

10. Hirschman SZ, Gerber M, Garfinkel E: DNA purified from naked intranuclear particles of human liver infected with hepatitis B virus. Nature 251:540-542, Oct 11, 1974

11. Robinson WS, Clayton DA, Greenman RL: DNA of a human hepatitis B virus candidate. J Virol 14:384-391, Aug 1974

12. Hirschman SZ, Vernace S, Schaffner F: DNA polymerase in preparations containing Australia antigen. Lancet 1:1099-1103, May 29, 1971

13. Kaplan PM, Greenman RL, Gerin JL, et al: DNA polymerase associated with human hepatitis B antigen. J Virol 12: 995-1005, Nov 1973

14. Dane DS, Cameron CH, Briggs M: Virus-like particles in serum of patients with Australia-antigen associated hepatitis. Lancet 1:695-698, Apr 4, 1970

15. Almeida J, Rubinstein D, Stott EJ: A new antigen-antibody system in Australia-antigen positive hepatitis. Lancet 2:1225-1227, Dec 4, 1971

16. Krugman S, Giles JP, Hammond J: Viral hepatitis type (MS-2 strain)—Studies on active immunization. JAMA 217:41-45, Jul 5, 1971

17. Zuckerman AJ: Hepatitis vaccine: A note of caution. Nature 255:104-105, May 8, 1975

18. Hollinger FB, Aach RD, Gituick GL, et al: Limitations of solid phase radioimmunoassay for HBAg in reducing frequency of post-transfusion hepatitis. N Engl J Med 289:385-389, Aug 23, 1973

19. Prince F, Brotman B, Grady GF, et al: Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis-B virus. Lancet 2:241-246, Aug 3, 1974

20. Feinstone SM, Kapikian AZ, Purcell RH, et al: Transfusion-associated hepatitis not due to viral hepatitis type A or B. N Engl J Med 292:767-770, Apr 10, 1975

Federal Support for Medical Schools

IN AN ARTICLE elsewhere in this issue, Dr. John E. Crowder considers the financing of medical education. Dr. Crowder briefly describes the current sources of support for the education and training of physicians, criticizes the findings of the Association of American Medical Colleges' (AAMC) Committee on Financing Medical Education and concludes that the shift of medical school funding from the private and local to the federal sector is at the heart of medical school problems. He proposes income contingent loans as a solution, particularly to increasing federal intervention into educational affairs. Attractive as the solution may appear, there are serious defects in this approach that become apparent in a closer examination of the complexity of the situation.

There is little question that since World War II, the federal government has provided substantial support for the educational, research and service activities of academic medical centers. Unfortunately, there is also little doubt that the federal government has become less and less a "passive contributor" and has sought more and

more "to shape both educational and fiscal policies of the nation's medical schools."

Federal funds were provided initially almost entirely for biomedical investigations. The success of the Office of Scientific Research and Development during wartime led the Congress to decide that improving our capabilities in preventing, diagnosing and treating disease by advancing knowledge in the biomedical sciences was in the public interest. To implement this decision, Congress subsequently enacted legislation to expand the scope of the National Institutes of Health (NIH). Appropriations for the NIH have increased from $46 million in fiscal year 1950 to $2 billion in fiscal year 1975. In keeping with our tradition that education and research should go hand in hand so that each could strengthen the other, the nation's academic medical centers became deeply involved in the expanding effort. In fiscal year 1974, medical schools expended $970 million for biomedical research and research training.

Although these funds have not directly supported the instruction and training of physicians, the increase in faculty size undertaken to meet the expanded biomedical research initiatives has greatly strengthened the milieu in which medical education is provided. However, the medical schools have become dependent on research grants for a part of the salary of their faculty members, many of them in tenured positions. The higher level of research activity has contributed to the financial problems of medical schools in another way. The funding agency never really covers the entire costs of the supported investigations and the institutions must devote a part of their own resources to the enterprise.

In 1963, the Congress finally reached a consensus that the federal government also had a role in the support of medical education. To a great extent, this decision was made in response to numerous studies that called for an expansion of medical school class size. There was a realization that given the magnitude of financing required, the necessary development of new schools and enlargement of existing schools would probably not take place without federal funds. The initial support for student assistance through loans and scholarships and matching construction funds was soon expanded to include grants for educational programs of the medical schools. Under the provisions of the Comprehensive Health Manpower Training Act of 1971, authorizations were provided for capitation grants of $2,500 per year per student to support educational programs in medical schools. Appropriations never reached the full authorization levels and the average capitation grant has never exceeded $2,000 per year. Eligibility for capitation grants required that the medical schools maintain the level of their general operating expenditures from other sources and increase their class size by five percent or ten students, whichever was greater. Expansion of class size has also been required for federal construction grants. Thus, the Congress has never provided unfettered contributions to the costs of medical education. It has always required the medical schools to carry out its mandates in return for support. The manpower bills which passed the House and Senate during the 93rd Congress without a resolution of differences in the legislation before adjournment and the bill recently passed by the House (H.R. 5546) increase the quid pro quos for capitation.

Federal funds also have an impact on the service programs of academic medical centers. In response to growing demands for the complex tertiary care provided by medical school faculties in teaching hospitals, the level of medical services provided by the academic medical centers has increased substantially. Income from professional fees earned by the faculty has become the fastest growing source of support for the centers during the past decade. As for all medical care, the federal share of reimbursement for the professional fees of the faculty and the costs of care in the teaching hospitals has risen sharply. Regulations related to reimbursement have had substantial effects on educational institutions. They have brought about changes in the nature of graduate medical education and slowed the introduction of advances flowing out of laboratory and clinical research into patient care.

It is clear that the Congress has seized upon the dependence of medical schools on federal funds to use them as convenient vehicles in confronting perceived problems it is unwilling or unable to deal with in a more direct manner. Although imposing onerous and intrusive conditions on the support of medical education through capitation grants is the most obvious route of federal intervention into medical school affairs, there are other programs through which the Congress can exert its will—the funding of biomedical research and the reimbursement of medical services through Medicare and Medicaid. There have been veiled

threats that these avenues will be used if medical schools refuse capitation grants because of the conditions required, and try to compensate for lost federal support by increasing tuition. In his valedictory speech, Caspar Weinberger, Secretary of Health, Education, and Welfare, recently warned of the "growing danger of all pervasive Federal Government." He laid most of the blame for "meddlesome" government to Capitol Hill. But overexuberant interpretation of statutory intent has brought excesses of authority for the federal agencies and they are out of or beyond control. The provisions incorporated in some legislation and the regulations that grow out of it give more and more reason for believing Richard Hofstadter's observation that reforming energies are easily "transmuted into mere peevishness."

If the federal government is involved in the capitalization of the income contingent loan program advocated by Dr. Crowder, it can restrict loans to students attending schools that meet criteria laid down by the Congress. The Rogers Bill (H.R. 5546) that has just passed the House does just this. The "capitation" funds supplied to a medical school must be repaid by the students after graduation, either in money or in service. The federal government will pay what amounts to additional tuition directly to the school under certain conditions and collect it later from the student. It is, in essence, an interest free loan which is available only to those who attend medical schools that agree to either increase their class size or carry out a substantial part of their clinical education and training in remote sites. There is little indication that given its present philosophy, the Congress would provide funds for support of medical education through any mechanism without attempting to use its leverage on the medical schools to carry out what it perceives to be the public purpose. The state governments are also beginning to attach equally intrusive requirements to the support they provide for both the publicly controlled and private medical schools.

There is little likelihood that the private sector would be able to provide the amount of funds needed to capitalize an income contingent loan program. The participation of commercial banks in the guaranteed student loan programs evidences a serious reluctance to invest in long-term loans with low interest return. The prospects of continuing high inflation rates makes such loans even less attractive to the banks. Inflation also makes it unlikely that the program could ever be fully capitalized to become a revolving loan fund.

If an income contingent loan program is not the solution, where do the answers lie to our current dilemma? The options are limited. Increasing tuition to cover the full costs will price medical education out of reach of all but the wealthy and halt efforts to broaden the socioeconomic levels of entering classes. There is little evidence that unrestricted gifts and grants from physicians, industry and foundations can be increased to the level required to eliminate dependence on government support. Other internal sources of support, such as income from the medical practice of the faculty, cannot be increased without producing severe distortions in the form and function of institutions. Reducing expenditures by sharp cutbacks in faculty and supporting services would have a serious impact on the quality of educational programs.

The current level of informed public debate has not permitted a thoughtful and objective assessment of the problems facing the nation's medical schools and the short-term and long-term implications of the outside pressures being exerted on the institutions by their financing sources. Until this occurs and those with the necessary leverage resolve the problems of accessibility and costs of health care, medical schools in the United States will face continuing difficulty in retaining the traditional freedoms of academic institutions which are critical to maintaining the excellence of their educational programs and their other contributions to improving health.

John A. D. Cooper, MD, PH D
President, Association of American Medical Colleges
Washington, DC

CASE REPORTS

Refer to: Reza MJ, Abbasi AS: Congestive cardiomyopathy in hypothyroidism. West J Med 123:228-230, Sep 1975

Congestive Cardiomyopathy in Hypothyroidism

MICHAEL J. REZA, MD
ABDUL S. ABBASI, MB
Los Angeles

THAT HYPOTHYROIDISM could cause congestive heart failure was first recognized by Zondek[1] in 1918. He reported four cases of myxedema associated with cardiomegaly, and the electrocardiographic changes of low QRS voltage and flattened or inverted T waves. Subsequently, it was shown that this entity of myxedema heart was refractory to digitalis and fluid restriction and that thyroid therapy was the treatment of choice.[2-4] Since then, pericardial effusions, and very rarely, pericardial tamponade[5,6] have been reported to occur in myxedema. Therefore, it has not always been clear whether cardiomegaly in patients with hypothyroidism was due to heart failure or represented a pericardial effusion.

With echocardiography it is possible to document the presence of a congestive cardiomyopathy,[7] and to rule out the coexistence of a significant pericardial effusion.

We have recently observed a patient presenting with a congestive cardiomyopathy without obvious cause. The patient was subsequently found to be hypothyroid. On serial echocardiograms, reversal of left ventricular dysfunction after thyroid replacement therapy was seen.

From the Department of Medicine, University of California, Los Angeles, Center for the Health Sciences.

The author was a Senior Resident in the Department of Medicine, University of California, Los Angeles, Center for the Health Sciences, when this paper was submitted.

Submitted January 31, 1975.

Reprint requests to: M. J. Reza, MD, UCLA Medical Center, 10833 Le Conte Avenue, Los Angeles, CA 90024.

Materials and Methods

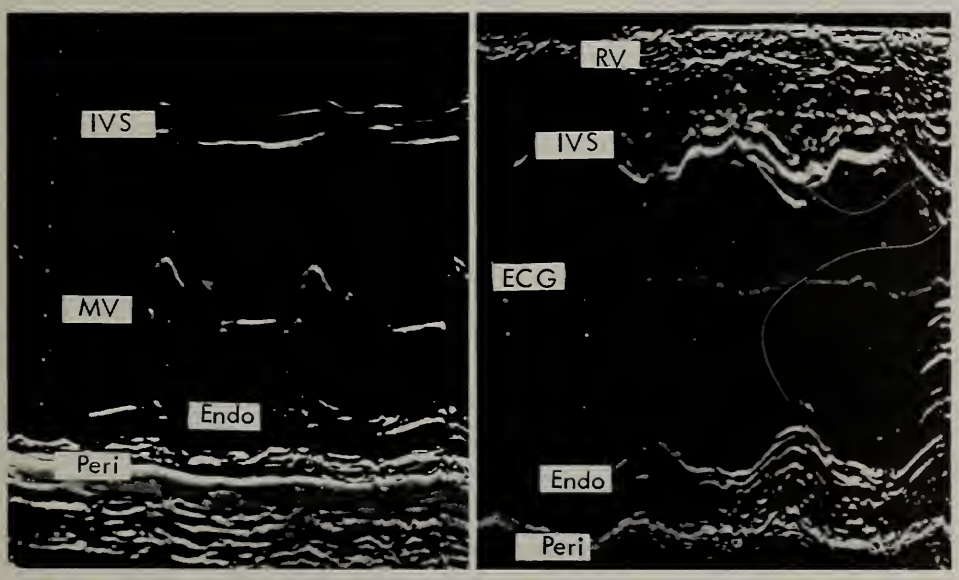
The echocardiograms were recorded with commercially available equipment using standard techniques described previously.[7-9] The measurement of left ventricular cavity size, posterior left ventricular wall motion and interventricular septal motion were recorded before and at various times after the institution of thyroid therapy.

Report of a Case

A 41-year-old woman previously in good health was admitted to the University of California, Los Angeles, Medical Center because of progressive dyspnea on exertion. Medical history and family history were unremarkable.

On physical examination, severe right- and left-sided congestive heart failure was noted; there were no clinical signs of pericardial tamponade. A small, smooth, firm, nontender thyroid gland without nodules was seen on examination of the neck. Findings on routine laboratory studies were normal. Results were negative or normal for the following studies: antinuclear antibody, LE cell preparation, Bence Jones protein, trypanosoma cruzi complement fixation antibody, serum iron and urinary heavy metal excretion. Results of thyroid function studies were as follows: serum T_4 Murphy-Pattee, 1 μg per 100 ml (normal 4 to 11); serum T_3 resin uptake, 27 percent (normal 25 to 35); serum thyrotropin stimulating hormone (TSH) 165 μg per ml (normal 0 to 10); I^{131} uptake 4 percent at six hours, 5 percent at 24 hours (normal 7 to 25 percent and 15 to 40 percent); serum antithyroglobulin titer (ATA) 1:15,625 (normal, less than 1:5); an I^{125} thyroid scan showed a small gland with patchy uptake. These findings were felt to be compatible with severe, primary hypothyroidism. On an x-ray film of the chest, pronounced cardiomegaly and pulmonary vascular congestion were seen (Figure 1 left). Findings on an electrocardiogram showed low voltage in the limb leads, isoelectric T waves in V_4-V_6 and poor R wave progression in the precordial leads. On phonocardiogram, prolonged preejection time of 0.19 seconds was noted. A QK_d time (the interval between the beginning of the QRS complex and the arrival of the arterial

Figure 1.—Chest x-ray studies of patient with hypothyroid cardiomyopathy. **Left,** before therapy, showing pronounced cardiomegaly. **Right,** six months after institution of thyroxine therapy, the heart size has returned to normal.



IVS = interventricular septum
MV = mitral valve
Endo = endocardium of posterior left ventricular wall
Peri = pericardium of posterior left ventricular wall
ECG = electrocardiogram
RV = anterior right ventricular wall

Figure 2.—Echocardiograms of patient with hypothyroid cardiomyopathy. **Left,** before treatment, showing the dilated left ventricle (between IVS and Endo) with a short-axis diameter of 6.5 cm (normal: less than 5.4 cm). Motion of interventricular septum and endocardial wall is notably reduced. A small posterior pericardial effusion is present. **Right,** after thyroxine replacement therapy. Left ventricular size is now normal (4.2 cm) and motion of the posterior left ventricular wall and interventricular septum are markedly improved.

pulse in the antecubital fossa at diastolic pressure)[10] was 330 milliseconds (normal 205 ± 15).

On an echocardiogram done on the second hospital day (Figure 2 left) notably decreased interventricular septal and posterior left ventricular wall motion were seen, as well as an increase in the left ventricular diameter (short-axis). A small posterior pericardial effusion (less than 200 ml) is present. A small anterior pericardial effusion could not be ruled out by echocardiographic findings; however, these findings excluded the presence of a large pericardial effusion. On a Technicium^{99} heart scan, cardiomegaly was noted and there was no evidence of a pericardial effusion.

The patient was initially treated with digoxin, furosemide and fluid restriction, but failed to show any improvement. When laboratory findings confirmed hypothyroidism, the patient was started on sodium levothyroxine (Synthroid®) 0.025 mg daily. The diogoxin and furosemide were then discontinued.

Results of serial echocardiograms showed

gradual improvement as the dosage of thyroxine was increased. Five months after initial evaluation, a daily maintenance dose of 0.225 mg of thyroxine was reached. The patient was clinically euthyroid and levels of serum T_4 and TSH were normal. On an echocardiogram taken at this time, a normal left ventricular cavity size was noted. However, because of slightly reduced posterior wall motion, the thyroxine was increased to 0.250 mg. Four weeks later, results of another echocardiogram (Figure 2 right) showed normal posterior wall motion. On an x-ray film of the chest taken at that time (Figure 1 right), a return to normal in heart size was seen. Findings on subsequent echocardiograms have continued to be normal, and the patient has been maintained on 0.250 mg of thyroxine.

Discussion

This case shows that hypothyroidism can produce the picture of a primary congestive cardiomyopathy, and that adequate thyroid replacement therapy completely reverses the left ventricular dysfunction. Echocardiographic documentation of congestive cardiomyopathy in hypothyroidism has not previously been reported.

The relationship between thyroid hormone and the heart is quite complex and has been reviewed elsewhere,[11] but it has become apparent that hypothyroidism results in a negative ionotropic effect on the myocardium. The clinical correlates of hypothyroid heart disease include: congestive heart failure, low voltage of all the complexes of the electrocardiogram, a prolonged preejection time and a prolonged QK_d time. One can now add the echocardiographic measurements of congestive cardiomyopathy to the above mentioned manifestations of hypothyroid heart disease.

Because of the frequent occurrence of pericardial effusions in these patients, an x-ray film of the chest may not give a true picture of cardiac size. Echocardiography appears to be a more accurate indicator of cardiac size and the response to therapy. Findings on serial echocardiograms in this case show that the improvement in cardiac function was related to thyroid hormone therapy. Although improvement shown clinically and roentgenographically after thyroid therapy in patients with hypothyroid heart disease is well known, echocardiographic documentation of this improvement, to the author's knowledge, has not been previously described. Because patients with hypothyroidism may have coexisting coronary artery disease, replacement therapy with thyroid hormone must be done in a careful and gradual manner. The possibility of precipitating or aggravating angina or congestive heart failure during replacement therapy must always be kept in mind. When normalization of cardiac function is not seen in patients with hypothyroid heart disease after they are rendered euthyroid with thyroid hormone replacement therapy, a physician should suspect the possibility of the presence of an additional process involving the heart—such as coronary artery disease.

Conclusion

It appears then, that hypothyroid heart disease is a reversible form of congestive cardiomyopathy. Because of the poor prognosis of cardiomyopathies in general, the author feels that hypothyroidism should be considered in the differential diagnosis in all patients who present with such a disorder. Echocardiography appears to be an excellent noninvasive method for assessing cardiac function and response to thyroxine therapy in patients with this entity.

Summary

A patient presenting with congestive heart failure and echocardiographic features of a congestive cardiomyopathy was found to be hypothyroid. L-thyroxine therapy resulted in dramatic clinical improvement, and results of serial echocardiograms showed reversal of the congestive cardiomyopathy pattern. It is suggested that hypothyroidism be considered in the differential diagnosis of patients presenting with a congestive cardiomyopathy, and that echocardiography can be used to assess cardiac response to therapy in patients with hypothyroid heart disease.

REFERENCES

1. Zondek H: Das Myxo-demherz. Munch Med Wochenschr 65: 1180-1182, 1918

2. Assman H: Das Myxo-demerz. Munch Med Wochenschr 66: 9, 1919

3. Fahr G: Myxedema heart. JAMA 84:345-349, 1925

4. Davis JC: Myxedema heart. Ann Intern Med 4:733-741, 1931

5. David PJ, Jacobson S: Myxedema with cardiac tamponade and pericardial effusion of "gold paint" appearance. Arch ntern Med 120:615-619, 1967

6. Spitzer S, Adam A, Mason D: Myxedema complicated by pericardial tamponade. Pa Med 73:33-34, 1970

7. Abbasi AS, Chahine RA, MacAlpin RN, et al: Ultrasound in the diagnosis of primary congestive cardiomyopathy. Chest 63: 937-942, 1973

8. Feigenbaum H, Popp RL, Wolfe SB, et al: Ultrasound measurements of the left ventricle. Arch Intern Med 129:461-467, 1972

9. Popp RL, Harrison DC: Ultrasonic echography for determining stroke volume and valvular regurgitation. Circulation 41:493-502, 1970

10. Rodbard S, Kramer RK: The timing of the arterial sounds in hypothyroidism. Am J Med Sci 252:404-412, 1966

11. deGroot WJ: Cardiomyopathy associated with endocrine disorders. Cardiovasc Clin 4:305-331, 1972

Refer to: Robb LG: Severe vasospasm following ergot administration. West J Med 123:231-235, Sep 1975

Severe Vasospasm Following Ergot Administration

LEON G. ROBB, MD, *Los Angeles*

COMPOUNDS CONTAINING ERGOT are used frequently in the treatment of migraine cephalgia. Ergot is also commonly used in the treatment of postpartum uterine hemorrhage, as well as in uterine subinvolution. The purpose of this paper is to present a case involving a young woman with a history of Raynaud's disease, and the events which followed administration of a single dose of a compound containing ergot.

Ergot alkaloids can exert toxic effects on both the vascular and nervous systems. Since 1930, there have been 41 cases reported of severe vascular effects in patients following administration of ergot compounds.[1-32] Thirty-four (83 percent) of the patients were under 45 years of age and most of them were women (78 percent), as shown in Table 1. In none was a secure diagnosis of preexisting vasospastic disease reported. In only one had a single dose of ergot compound been given, as in our case.

Report of a Case

A 34-year-old woman was first admitted to Hollywood Presbyterian Medical Center with complaint of severe pain and tenderness of the distal right index finger. The finger was found to be cyanotic. Eight years previously, the patient had been told that she had Raynaud's disease. The major finding, at that time, was mottling of the lower extremities, especially in cold weather. The patient was advised to stop smoking; however, this advice was not followed. The changes in the finger were noted six weeks before admission, following an emotionally traumatic incident. Sensation in the finger was intermittently numb or burning. Color changes varied from pale to grey. There was moderate improvement following administration of vasodilating drugs.

On examination, the distal phalanx was seen to be cyanotic, no digital pulses were present and the skin temperature of the digit was 25°C (77°F). The only other significant findings were mottling of the lower extremities and a suggestion of digital clubbing. Skin temperature measurement and impedence plethysmography were carried out. Impedence pulses in the arms showed substantial abnormalities in pulse contour (Figure 1a). The right arm pulse wave appeared damped. There was substantial reduction in ejection velocity and prolongation of pulse duration in the forearm and at the wrist. Skin temperature suggested vasoconstriction.

In order to evaluate vasoconstriction response (Figure 2), ice water submergence was carried out. The legs had pronounced changes in tempera-

TABLE 1—*Reported Cases of Ergot Induced Ischemia*

Reported by	*Number of Cases*	*Sex*	*Age*	*Year*
Antoine[1]	1	F	21	1930
Gould, Price, Ginsberg[2]	1	F	52	1936
Yater, Cahill[3]	1	M	64	1936
Fairbairn[4]	2	M, F	52, 64	1958
Cameron, French[5]	1	F	45	1960
Young, Humphries[6]	1	F	42	1960
Johnson[7]	2	F	34, 35	1961
Ureles, Rob[8]	1	M	36	1963
Bross, et al[9]	1	F	20	1963
Cranley, et al[10]	1	F	30	1963
Kramer, Hecker, Lewis[11]	1	F	54	1965
Engle, Silvertssen[12]	2	F	39, 25	1965
Johnson[13]	1	F	44	1966
Glazer, Myers, Davies[14]	1	M	33	1966
Tator, Heimbecker[15]	1	M	52	1966
Katz, Massry[16]	1	F	33	1966
Fagerberg, Jonulf, Sandberg[17]	1	F	42	1967
Ahlgren, et al[18]	1	F	68	1968
Haynes, Davis[19]	1	F	38	1968
Bertho, Ratte, Joan[20]	1	F	62	1969
Sutton, Preston[21]	2	M, F	33, 29	1970
Felix, Carroll[22]	1	F	39	1970
Dominic, Lysight[23]	1	F	18	1970
Fedotin, Hartman[24]	1	F	40	1970
Yao, Goodwin[25]	1	F	24	1970
Syme[26]	1	F	28	1971
Bagby, Cooper[27]	2	F	42, 59	1972
Manachem, Eger[28]	1	M	36	1972
McLoughlin, Sanders[29]	1	F	39	1972
Hessen, Kromann-Anderson, Madsen[30]	5	F	31, 33, 34 40, 41	1972
Richter, Banker[31]	1	F	39	1973
Carl, Goldberg et al[32]	1	F	50	1974

From the Anesthesia Section, Hollywood Presbyterian Medical Center, Los Angeles.

Submitted December 23, 1974.

Reprint requests to: L. G. Robb, MD, 5224 Los Adornos Way, Los Angeles, CA 90027.

ture induced by the cold. The decrease in temperature in the thighs was 1.4°C, calves 1.6°C, ankles 1.8°C, great toes 8.3°C, middle and small toes 7.4°C. Significant decline in skin temperature occurred in the entire right arm with minor temperature decrease in the left. Cigarette smoking produced negligible change in the skin temperature from −0.1°C proximally to −1.2°C distally, after cigarette use.

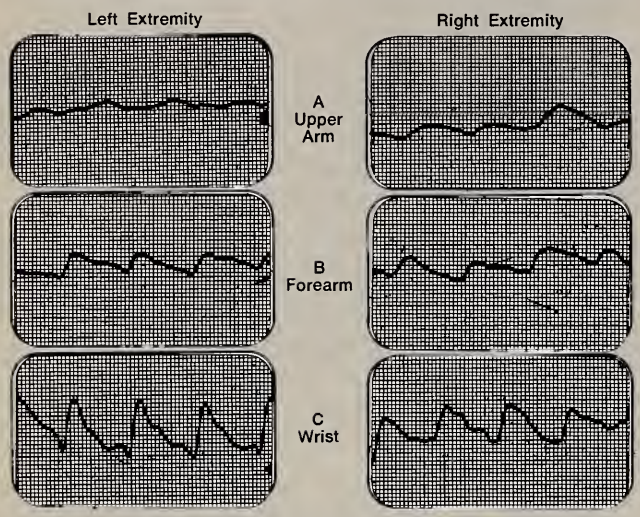


Figure 1.—Impedence pulses in arm. Pulse contours are greatly diminished. The right arm pulse wave is damped. Ejection velocity is reduced and the pulse duration is prolonged.

The presumptive diagnosis of Raynaud's disease was made and the patient was given a cervicothoracic (stellate) ganglion chemical sympathetic block on the right. There was immediate reversion of cyanosis and relief of pain and tenderness. Skin temperature increased (Figure 3) and on plethysmography pronounced improvement was noted (Figure 4). This effect persisted longer than the duration of the block. The patient was discharged as improved, with no onycho cyanosis and only minimal tenderness in the distal phalanx.

Two years later she was admitted again with severe pain, cramping and icy coolness of both legs and the right arm. One week previously, the patient had been treated for menorrhagia by a physician at an outside medical clinic. An intramuscular injection of ergotrate had been administered, which caused extremity pain. The pain increased in intensity, requiring admission to the hospital.

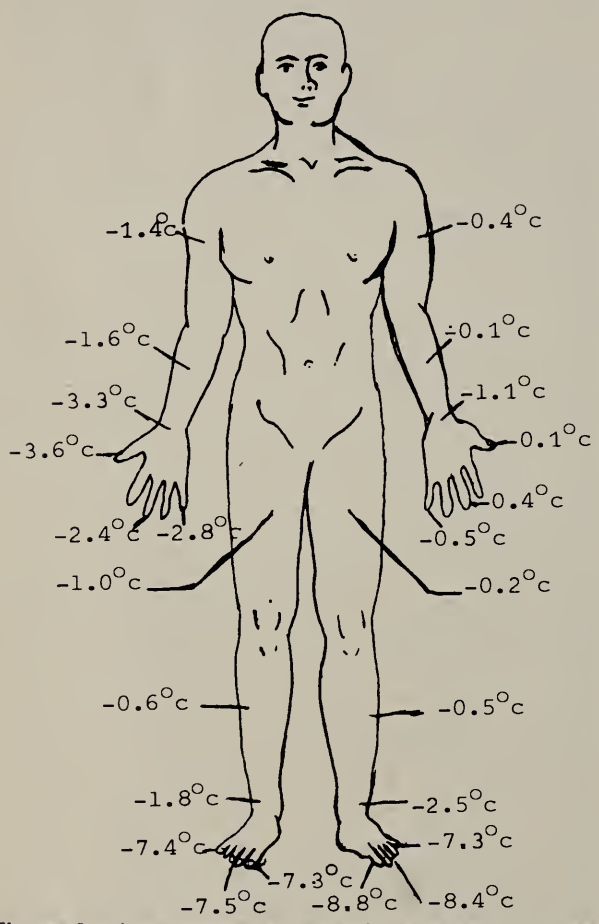


Figure 2.—Ice water emergence for evaluation of vasoreactivity. Temperature change is noted at various sites.

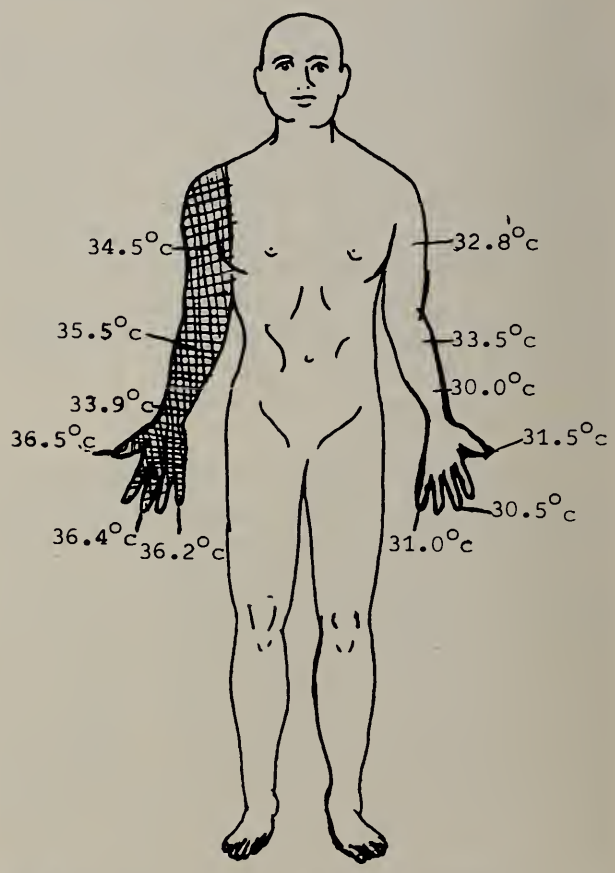


Figure 3.—Cervicothoracic (stellate) ganglion block on right. Increase in skin temperature from blocked to nonblocked extremity is shown.

Administration of vasodilating drugs and tranquilizers did not appear to alter the progression of the vasospasm. The extremities were found to be extremely cold; the color was plethoric proximally to cyanotic distally. The veins were collapsed and could not be filled by the usual measures. The peripheral arterial pulsations were all palpable, but notably diminished. The dorsalis pedis pulse was absent.

A right cervicothoracic chemical sympathetic block (Stellate ganglion) was carried out with bupivicaine 0.25 percent (Marcaine®), a new long-acting local anesthetic. The block resulted in immediate pronounced venodilatation and relief of arterial spasm. The skin temperature increased and the pain was relieved. A lumbar epidural injection of bupivicaine 0.25 percent was given to effect a chemical sympathectomy of the legs. This blockade was continued by insertion of a teflon catheter into the epidural space. Intermittent doses of the local anesthetic were required every six hours to relieve the spasm, afford vasodilatation and relieve pain. The legs were warm to the touch and did not cause discomfort, and sensation was preserved. The patient was capable of full motor function, including walking. The arterial pulsations were subjectively felt to have increased. The epidural catheter was removed in 24 hours.

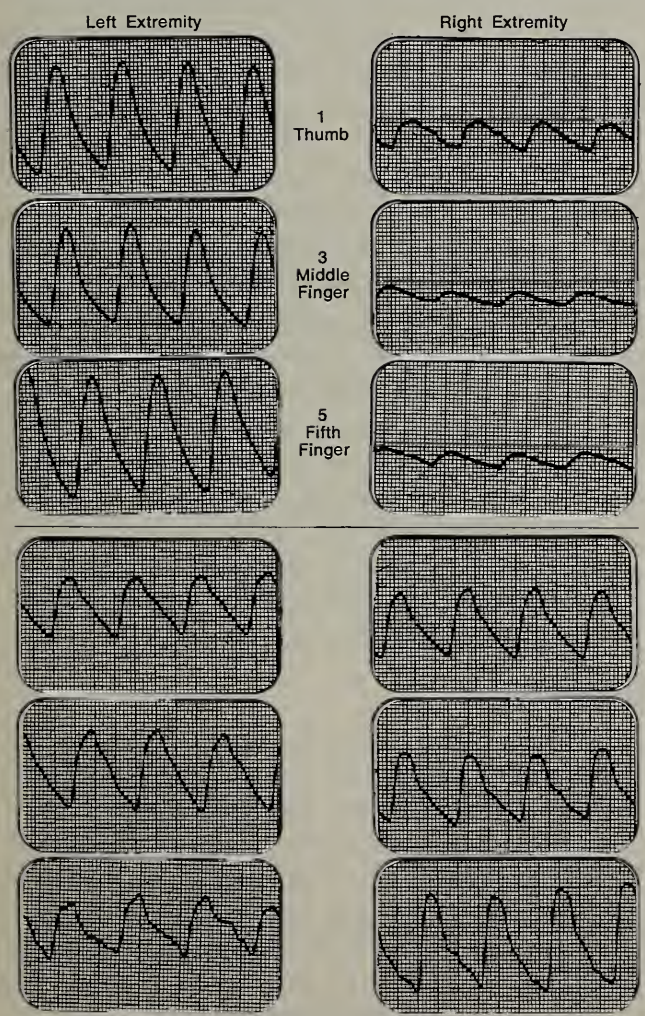


Figure 4.—Upper, Preblock plethysmogram in upper extremities. Digital pulses show diminished contour on the right. **Lower,** Postblock plethysmogram shows dramatic improvement. The pulse contour has returned to normal. Amplitude in the fifth finger is even greater in the right.

Two days following this removal, there was resurgence of symptoms in the left leg and right arm. The stellate ganglion blockade and the continuous lumbar epidural was once again administered, with excellent relief. The patient was discharged 24 hours later, improved.

Comment

To the best of our knowledge, there are no reported cases of ergot administration in patients with Raynaud's disease. Perhaps the cases of reported hypersensitivity or innate sensitivity to ergot are subclinical cases of Raynaud's disease. Other undiagnosed vasoreactive disorders might become evident after the administration of vasospasm-provoking agents.

There are several cases in the literature which illustrate the vasospastic danger after ergot administration. In one, there was severe gangrene of the legs following ergotrate given orally for metrorrhagia in a 20-year-old patient.[9] In another case, severe disability occurred in a 30-year-old nurse, following administration of ergotamine tartrate (Cafergot®) for headaches.[10] This led to four-extremity gangrene, which was resistant to papavarine, tolazoline and heparin. Sympathetic blockade was withheld because the physician believed that "this type of vasospasm was not neurogenic," and would not respond. General anesthesia given for debridement and vascular exploration did not alter the vasospastic consequences.

In many of the cases, the ischemia was resistant to drug therapy; one patient reportedly responded to spinal anesthesia.[13] Besides drug therapy, patients have been treated with various types of sympathetic affector ablation. These include chemical blockades by spinal anesthesia,[13,23,29] single dose epidural or continuous epidural anesthesia,[18,28,29] stellate ganglion blockade[11,15,18] and paravertebral sympathetic blockade.[9,12] Two cases were treated with periarterial sympathectomy[6,20] and two others by surgical sympathectomy.[6]

The effects of ergot in low dosages can be toxic in patients with liver disease.[2,3] One such case re-

ported is that of a 23-year-old woman who was given ergotamine tartrate (Gynergen®) 1 mg three times a day for five days.[16] In the interim, infectious hepatitis developed. Intense vasoconstriction of the small and medium-sized arterioles occurred with local thrombus formation. The liver is the major site of detoxification of this substance, and normally tolerated doses may lead to ergot poisoning when abnormal hepatocellular function exists. This is the reason that ergot compounds are no longer used for the treatment of pruritus associated with jaundice.

Therapeutic doses of ergotamine tartrate (Cafergot®) were given to two young women who had a possible "predisposing hypersensitivity and who developed arterial insufficiency." Sympathetic blocks were reportedly helpful by increasing skin temperature, but otherwise were of "questionable benefit." An "innate sensitivity" was given as the cause of these two cases reported in the *British Medical Journal*.[25]

The classic description of Raynaud was of a disorder in which pallor, cyanosis and rubor of the distal portion of the extremities occurred. If this is associated with another disease (such as scleroderma, lupus erythematosis, rheumatoid arthritis, arteriosclerosis obliterans or thromboangitis obliterans), it is known as Raynaud's phenomenon.

All the criteria in the Gifford and Hines study[33] were present in our patient: (1) there were episodes of pallor, cyanosis and rubor precipitated by cold or emotion; (2) symptoms were bilateral; (3) gangrene was absent or of a minimal degree, limited to the distal cutaneous surfaces; (4) no underlying cause could be found for the preexisting vasospastic episodes, and (5) duration of the symptoms was two years or longer. In addition, the disease is five times more common in women than in men.

The cause of the disease is as yet unknown. A mechanism that has been proposed is digital artery hypersensitivity to vasomotor effects of nervous system hyperactivity. High blood viscosity and elevated plasma fibrinogen concentration have been found in a large percentage of these patients.[34] The significance of this has not been explored.

The mechanism causing pallor is precapillary arteriolarspasm and the reduction of red cells in cutaneous capillaries. Cyanosis is due to stasis of deoxygenated blood in the skin capillaries. Postcapillary constriction allows the stasis to occur. When there is reactive vascular dilatation, the oxygenated blood circulates to the vessels causing the characteristic rubor. This may be due to the vessel wall being affected by anerobic metabolic products (such as lactate, pyruvate and the like) following the initial period.

In Raynaud's disease, the prognosis is usually excellent. Ischemia of a major portion of a limb allegedly never occurs unless, of course, other factors are present. Amputation has been reported in fewer than 0.4 percent of the cases.[33] Frank tissue hypoxia may ensue whenever a vasoconstrictor is used in a patient in whom there is a propensity for vasospasm.[33,34] The vasospastic potential in these "hypersensitive" patients is so profound that a single dose may eventuate into severe consequences.

It is well known that norepinephrine, epinephrine and nicotine synergize the vasoconstrictor activity of ergot. Parenteral administration of ergot is used to produce uterine contractions in postparturient patients. If vasopressors have been administered previously for hypotension, constriction of major organ arterial blood supply and disastrous hypertension can occur.

Physicians using compounds containing ergot are often unaware of the potentially severe consequences of its application in some patients, especially those with vasospastic disorders. The underlying mechanism in the previously mentioned cases, which were labeled with drug hypersensitivity or so-called innate sensitivity, may have been subclinical or undiagnosed cases of Raynaud's disease. Remembering that it is important to take a careful history before administering a drug, as well as having complete knowledge of the drug's pharmacological effects, should prevent this type of misadventure.

Summary

A 34-year-old woman presented with severe menorrhagia, for which a single dose of a compound containing ergot was administered. As a consequence of the therapy, severe vasospastic symptoms developed. The vascular insufficiency was relieved by chemical sympathectomy by lumbar and cervicothoracic sympathetic ganglion blockade.

REFERENCES

1. Antoine T: Gangrene of leg after confinement caused by single injection of ergotamine. Arch Gywak 139:492, 1930

2. Gould SE, Price AE, Ginsberg HI: Gangrene and death following ergotamine tartrate therapy. JAMA 106:631, 1936

3. Yater WM, Cahill JA: Bilateral gangrene of feet due to ergotamine tartrate used for pruritis of jaundice. JAMA 106: 1625-1631, 1936

4. Fairbairn JF: Severe arteriospastic disease secondary to use of ergot preparations. Med Clin of N.A. 42:971-974, 1958

5. Cameron EA, French EB: St. Anthony's fire rekindled, gangrene due to therapeutic dose of ergot. Br Med J 11:28, 1960

6. Young JR, Humphries AW: A severe ateriospasm after use of ergotamine tartrate suppositories. JAMA 175:1141-1145, 1961

7. Johnsson KA: Angiography in 2 cases of ergotism. Acta Radiol 57:280-284, 1962

8. Ureles AL, Rcb C: Ischemia of a limb complicating methysergide meleate therapy. JAMA 183:1041-1042, 1963

9. Bross W, Cisek T, Caereda T, et al: Gangrene of the legs after ergotrate by mouth. Lancet 12:856, 1963

10. Cranley J, Krause R, Strasser E, et al: Impending gangrene of four extremities secondary to ergotism. N Engl J Med 269:727-729, 1963

11. Kramer RA, Hecker SP, Lewis BI: Ergotism. Radiology 84: 308-311, 1965

12. Enge I, Silvertssen E: Ergotism due to therapeutic doses of ergotamine tartrate. Am Heart Journal 70:665-670, 1965

13. Johnson TD: Severe peripheral arterial constriction, acute ischemia of the lower extremity with use of methysergide and ergotamine. Arch Intern Med 117:237-241, 1966

14. Glazer G, Myers KA, Davies ER: Ergot poisoning. Postgrad Med J 42:562-568, 1966

15. Tator CH, Heimbecker RO: Unilateral ischemia due to ergot. Canadian Med J 95:1319-1321, 1966

16. Katz AI, Massry SG: Arteriospasm after ergotamine tartrate in infectious hepatitis. Arch Intern Med 118:62-64, 1966

17. Fagerberg S, Jorulf H, Sandberg CG: Ergotism. ACTA Med Scand 182:769-792, 1967

18. Algren I, Haeger K, et al: Imminent gangrene of the leg following ergot poisoning. Angiology 19:359-361, 1968

19. Haynes CD, Davis ME: Ergotism—report of a case with localized arteriographic changes. Angiology 19:199-202, 1968

20. Bertho E, Ratte I, Joan JD: Iatrogenic ergotism—report of a case. Angiology 20:455-459, 1969

21. Sutton D, Preston B: Angiography in peripheral ischemia—report of a case. Br J Radiol 43:776-780, 1970

22. Felix RH, Carroll JD: Upper limb ischemia due to ergotamine tartrate. The Practitioner 205:71-72, 1970

23. Dominic C, Lysight R: Threatened gangrene in pregnancy caused by root alkaloids. J Irish Med Assoc 63:446-447, 1970

24. Fedotin MS, Hartman C: Ergotamine poisoning producing renal artery spasm. N Engl J Med 283:518-520, 1970

25. Yao ST, Goodwin DP: A case of ergot poisoning. Br Med J 3:86-87, 1970

26. Syme J: Clinic angiographic diagnosis. Australian Radiol 15:45-51, 1971

27. Bagby R, Cooper RD: Angiography in ergotism. Am J Roent 116:179-185, 1972

28. Manachem H, Eger M: Angiography in diagnosis of ergotism. Radiology 103:89-90, 1972

29. McLoughlin M, Sanders R: Ergotism causing peripheral vascular ischemia. Rocky Mountain Med J 69:45-49, 1972

30. Hesson IB, Gromann-Anderson C, Madsen B: Peripheral arterial insufficiency during ergotamine treatment. Danish Med J 19:236-239, 1972

31. Richter AM, Banker VP: Carotid ergotism. Radiology 106: 339-340, 1973

32. Carliner NH, Denune DP, Goldberg LI, et al: Sodium nitroprusside treatment of ergotamine induced peripheral ischemia. JAMA 227:308-309, 1974

33. Gifford RW, Hines EA: Raynaud's disease among women and girls. Circulation 16:1012, 1957

34. Pringle R, Walder DN, Weaver JPA: Blood viscosity and Raynaud's disease. Lancet 1:1086, 1965

35. VanStorch TJE: Complications following the use of ergotamine tartrate. JAMA 111:293, 1938

Management of Sleep Disorders in the Depressed Patient

What we tend to do with our severely depressed patients is either give them an antidepressant late in the day or give them a single dose of chlorpromazine (Thorazine®) or thioridazine (Mellaril®), 50 or even 100 mg if that turns out to be necessary, at bedtime. A point of fact—the tricyclics do a very good job of improving sleep and they do it fairly rapidly; it is one of their earliest benefits, long before the mood begins to improve, if it does. You might consider, if you are going to put your patient on amitriptyline (Elavil®), for example, that you give most of the dose around bedtime. The other thing is to tell him that his sleep will improve shortly. People can stand a lot of discomfort if they have some reason to think things will get better.

—MERLIN H. JOHNSON, MD, *Seattle*

Extracted from *Audio-Digest Family Practice,* Vol. 23, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Trauma Rounds

Chief Discussant
THEODORE R. SCHROCK, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Schrock TR: Injuries of the colon and rectum (Trauma Rounds). West J Med 123:236-239, Sep 1975

Injuries of the Colon and Rectum

MICHAEL COUGHLIN, MD:* The patient is a 38-year-old woman presenting with an injury to the rectum. She entered the emergency room complaining of pain in the rectal area 24 hours after a piece of plastic fruit was inserted into the rectum during intercourse. Twelve hours after the insertion of the plastic foreign body, she noted rectal bleeding and pain in the perineum followed by lower abdominal pain. On physical examination in the emergency room, the patient was found to be in moderate distress from lower abdominal pain. Temperature was 37°C (98.6°F). Examination of the head, neck and chest showed no abnormalities. The abdomen was noted to be tender in the lower quadrants, with local rebound. Bowel sounds were absent.

Pelvic tenderness was confirmed on pelvic examination, and a laceration in the posterior fornix of the vagina was noted. On rectal examination, there was a slight amount of blood on the examining finger, and a laceration of the anterior rectum approximately 7 cm from the anal verge was seen with the sigmoidoscope. The rectal laceration appeared to communicate with the peritoneal cavity. Initial laboratory data included a hematocrit of 46 and a leukocyte count of 14,000 with a shift to the left. Findings on urinalysis were within normal limits. Air beneath both diaphragms was noted on plain films of the abdomen.

Shortly after admission, exploratory laparotomy was done. A 3 cm laceration of the anterior rectal wall was found, and there was gross fecal contamination in the pelvic portion of the peritoneal cavity. The rectal tear was oversewn, an end sigmoid colostomy and a mucous fistula were done, and the distal colonic segment was irrigated copiously. No drains were placed. The postoperative course was benign.

DONALD D. TRUNKEY, MD:† *We are privileged today to have Dr. Theodore Schrock, Assistant Professor of Surgery at the University of California, who has considerable experience in colon and rectal surgery, to discuss injuries of the colon and rectum.*

THEODORE K. SCHROCK, MD:‡ The goals of therapy in patients with injuries of the colon and rectum are patient survival, minimal morbidity, intestinal continuity and rehabilitation in the shortest possible time. Sometimes we can achieve all of these objectives with a single procedure.

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

*Intern, Trauma Service, San Francisco General Hospital.

Reprint requests to: D. D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco, CA 94110.

†Assistant Professor of Surgery, University of California, San Francisco; Chief of Surgery, Mission Emergency Hospital, San Francisco.

‡Assistant Professor of Surgery, University of California, San Francisco.

Often, however, we must sacrifice intestinal continuity or duration of disability for the sake of patient survival.

The operative procedure which will best meet these objectives depends on many factors: (1) the type of trauma—penetrating or blunt—and if it is penetrating, whether the missile was high or low velocity; (2) the number and kinds of associated injuries—very important factors; (3) the severity and duration of shock; (4) age of the patient; (5) interval from wounding to beginning the operation—seldom a problem in civilian injuries; (6) the portion of the large bowel which is injured—right colon, left colon or rectum; (7) the characteristics of the colonic wound—size, shape, devitalized or contused tissue, hematoma, mesenteric or antimesenteric border; (8) extent of fecal contamination; (9) preexisting disease or drug therapy which may influence healing.

Although these factors are many in number, three common denominators largely determine the outcome of treatment of colorectal wounds: infection, oxygen delivery and the synthesis of collagen. That closure or anastomosis is technically well carried out is important of course, but closures will leak in the presence of infection, poor blood supply or impaired collagen synthesis despite technical excellence.

Infection is a major reason for failure of anastomotic healing in the large bowel. While patients operated upon electively are given a "bowel prep" to evacuate the fecal mass and suppress fecal flora, there is fecal loading of the colon in trauma patients at the time of injury. Contamination by spillage of feces through the defect is invariably present to some degree, and the extent of contamination helps determine whether infection will become established. Another factor which promotes local infection is trauma to tissues adjacent to the colon. Blood in the peritoneal cavity is known to potentiate bacterial virulence in experimental animals and in patients. Infection at a colonic suture line causes lysis of collagen by acid cathepsins and lysosomal enzymes and thrombosis of small blood vessels in the bowel wall. Both factors weaken the bowel and contribute to dehiscence of the suture line. Collagenase, another enzyme which lyses collagen, probably plays a minor role in this process. The chances of infection are minimized by evacuation of fecal material at operation and by instillation of antibiotics into the peritoneal cavity. Despite these measures, postoperative sepsis with associated suture line dehiscence is frequent and in some cases of severe trauma it is almost predictable.

Oxygen delivery to the healing colon is an extremely important determinant of outcome. Blood supply to the colon may be impaired by traumatic severance or surgical ligation of mesenteric vessels, or by hematoma or contusion in the bowel wall. Delivery of oxygen is impaired by hypotension, cardiopulmonary disease, or other factors. In a severely traumatized patient in whom there are multiple injuries to other organ systems, there most likely is impaired oxygen delivery to the bowel wound. Poor blood supply reduces healing capacity and reduces resistance to infection.

Synthesis of collagen by fibroblasts contributes importantly to increasing tensile strength of a colonic wound beginning on about the third day. Anything which limits this process—advanced age, adrenal corticosteroids or malnutrition—jeopardizes the patient.

I mentioned earlier that determining which anatomic portion of the large bowel is injured is important in selecting the method of surgical treatment. In a sense, the large intestine can be considered as three organs: right colon, left colon and rectum. Each requires a different type of management. In general, there is more latitude in treating injuries of the right colon compared with the left colon. The lumen is larger, the intraluminal pressures are lower, the fecal content is more liquid, and there are fewer bacteria per ml of feces and proportionately fewer anaerobes in the right colon. Perhaps for these reasons as well as inherent healing properties, anastomotic dehiscence occurs less often on the right than on the left.

The rectum heals least well, and the most important reason is probably the absence of a peritoneal coat on the lower rectum. Peritoneum is able to dispose of small numbers of bacteria which are present after injury or indeed after elective operation, and if the inoculum is not too large, infection will not occur. Low in the rectum where there is no peritoneum, however, these defenses are not available, and suture lines are notoriously prone to leakage because of infection.

The importance of these factors was apparent in the review of trauma to the large bowel which Dr. Norman Christensen and I did several years ago. We found 147 patients in whom there were perforating injuries. Most of the injuries were stab or gunshot wounds, but in ten patients they re-

TABLE 1.—*Effect of Associated Injuries on Outcome of Colorectal Trauma*

	Number of Other Organ Systems Injured		
	0-1	*2-3*	*4-9*
Number of patients	63	33	17
Mortality (percent)			
Immediate	0	6	47
Late	5	3	44
Wound infection (percent)	18	16	44
Abdominal abscess (percent)	14	16	44
Hospital days			
Initial	16	22	29
Subsequent	4	8	32
Total	20	30	61

TABLE 2.—*Primary Suture of Perforating Injuries of the Colon*

	Location of Perforation			
	Right	*Transverse*	*Left*	*Total*
Number of Patients	22	22	19	63
Late Deaths	2	0	1	3
Anastomotic leak	0	0	2	2
Hospital days	11	14	13	12

sulted from other causes. Rectal perforation in one patient was from an enema administered with a fire extinguisher, and in another patient rectal injury was due to an enema with a garden hose; both injuries resembled that in the patient presented today—who was injured by a foreign body in the rectum.

The overall mortality rate in our review was 15 percent; 8 percent of patients died within 24 hours due to hemorrhage from associated injuries, and 7 percent died later of septic complications. In 50 percent of patients there were significant complications (36 percent of these were infections), and in 18 percent of patients there were wound infections.

The influence of associated injuries on outcome was strong. Table 1 lists the mortality rate, infection rate and length of stay in hospital according to the number of other organ systems which were injured. It is apparent that there are two groups of patients: (1) those in whom there was solitary injury to the large bowel, often resulting from stab wounds, low velocity missiles or miscellaneous causes such as rectal perforation from foreign body and (2) those patients in whom there was catastrophic trauma to multiple organs. The former did well, the latter fared poorly. The same correlation with outcome was found when patients were analyzed according to the severity of shock or the extent of fecal contamination.

F. William Blaisdell, MD:* *Dr. Schrock, would you describe your management of injuries in specific areas of the colon?*

Dr. Schrock: The principal methods of management of wounds of the large bowel are as follows: (1) primary suture, (2) exteriorization of a primarily sutured wound, (3) primary suture with proximal decompression or diversion, (4) exteriorization of the wounded colon, (5) resection of the injured colon with temporary end colostomy and distal mucous fistula or Hartmann's pouch and (6) resection with primary anastomosis. Various other techniques such as obstructive resection may be used occasionally. Most of our experience was with primary suture, exteriorization of sutured perforations and resection without anastomosis. Table 2 lists the cases of primary suture. The results in wounds of the right or transverse colon were excellent, but there were problems with the left colon. One must realize that patients managed in this way were highly selected; in these patients there were small, simple wounds, no or only minor associated injuries, minimal fecal contamination and all the other factors favorable to primary healing. The exercise of surgical judgment requires that all these factors be weighed. I recommend against primary suture of wounds in the left colon and in these other situations: wounds on the mesenteric border, and wounds of the colon which lie against retroperitoneal hematomas or injured liver, pancreas, duodenum or kidney.

Primary suture of a wound accompanied by exteriorization of the injured segment was popular briefly in this hospital and is still advocated by some authors. The rationale is that if the wound heals, the colon is simply replaced into the abdomen, but if the suture line leaks, the leak is outside the abdomen and thus forms a colostomy. In our series, in 15 of 19 patients so treated conversion to colostomy had to be done because of leak (11 patients) or obstruction (4 patients). The ideal milieu for colonic healing is the peritoneal cavity; healing of exteriorized colon is unsatisfactory, and such colostomies are bulky and difficult to manage if there is unsatisfactory healing. I do not recommend this approach.

Resection with anastomosis may be used in favorable cases of injury to the right colon but

*Chief of Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco.

should not be used in the left colon. With wounds of the left colon or with multiple associated injuries, it is best to resect without anastomosis.

A PHYSICIAN: *Is your management of rectal injuries different from that of colon injuries?*

DR. SCHROCK: Yes. Rectal injuries should be managed by diverting colostomy and drainage of the presacral space, and through emptying of feces from the rectum by irrigation at the conclusion of the operation. If possible, the rectal injury should be closed. Associated injuries of the genitourinary tract must be sought and treated. The patient presented today had an isolated laceration of the rectum above the peritoneal reflection. It was handled appropriately and with a good result; had the laceration been below the peritoneal reflection, it should have been drained.

Historical Note

FOTHERGILL'S NEURALGIA

THE EARLIEST DESCRIPTION of trigeminal neuralgia or tic douloureux was by Fothergill, published by The Medical Society, London. Fothergill wrote in 1779 [Fothergill J: Of a painful affection of the face. Medical Obs & Inquiries 5:129-142, 1779]:

> This affection seems to be peculiar to persons advancing in years, and to women more than men. I never met with it in any one much under forty, but after this period, no age is exempt from it.
>
> The case does not occur very frequently. I can recollect but about fourteen instances in the course of my business.
>
> From imperceptible beginnings, a pain attacks some part or other of the face, or the side of the head; sometimes about the orbit of the eye, sometimes the *offa malarum,* sometimes the temporal bones, are the parts complained of. The pain comes suddenly, and is excruciating; it lasts but a short time, perhaps a quarter or half a minute, and then goes off; it returns at irregular intervals, sometimes there are two or three repetitions in a few minutes.
>
> The kind of pain is described differently by different persons, as may be reasonably expected; but one sees enough to excite one's compassion if present during the paroxysm.
>
> It returns full as often in the day as in the night. Eating will bring it on some persons. Talking, or the least motion of the muscles of the face affects others. The gentlest touch of a hand or handkerchief will sometimes bring on the pain, whilst a strong pressure on the part has no effect.

This classic description is as accurate as that available 200 years later. He further differentiated this from other conditions of the face.

Dr. Fothergill found no reference to such a disorder except in an earlier volume of Medical Observations and Inquiries (V. 3, 1767) in a paper discussing the use of hemlock in relief of pain, one patient had a "painful disease affecting the face."

ACKNOWLEDGMENT: I am indebted to the Francis A. Countway Library of Medicine, Harvard Medical School, for allowing the use of the rare book collection.

RONALD D. GREENWOOD, MD
Children's Hospital Medical Center
Boston

Informed
OPINION

Refer to: Stubblebine JM: Recommendations for some Medi-Cal improvement (Informed Opinion). West J Med 123:240-246, Sep 1975

Recommendations for Some Medi-Cal Improvement

J. M. STUBBLEBINE, MD, *Greenbrae, California*

EDITOR'S NOTE: *The author's professional background includes six years as Program Chief, Community Mental Health Services, Department of Public Health, San Francisco. This was followed by the positions of Director of Mental Hygiene, Director of Health, and Director of Aging at the State level from 1971 to 1974. In the latter two positions he was the first appointee. The views expressed are solely his own and do not represent those of any government agency at any time.*

THE MEDI-CAL part of the California State budget is often fair game for critics, and the potshots seem to recur with almost predictable periodicity. The criticisms reach a peak during the governor's and legislature's budget considerations and during the annual meeting of the California Medical Association. Both sources have recently, like volcanoes threatening to erupt, been sending out warning puffs of smoke. The puffs may or may not coalesce into a storm cloud with thunder and lightning, but they do tend to obscure basic facts and to impede constructive changes. Because the Medi-Cal program is so big, so complex and so important, and because all parties are basically altruistic but of different viewpoints, the whole issue can get overcharged with an electric tension. Unfortunately this may cause government on the one hand and the health professions on the other to appear in an adversary relationship, and progress suffers. Excessive dynamic tension in one person can cause catatonia; in a societal program so major as health services it may also paralyze action. And the society as surely as an individual person is suffering unnecessary hurt and pain.

The times now clearly call for bold measures in order to meet both fiscal needs and amount and quality of health services. Preparation for possible national health insurance also demands a new look at the basic goals of the Medi-Cal program and especially its administrative structures. If Medi-Cal were a patient, we would say it is basically sound but acutely ill and getting worse—and immediate, vigorous, but careful treatment is needed. The general approach of both the Reagan and Brown administrations has been small-scale palliative, not curative nor rehabilitative; both have tended to make fine adjustments in the components of the present system. What is needed is major and fundamental change in the system itself, maybe even radical

From the Department of Psychiatry, Ross Valley Medical Clinic, Greenbrae, CA.

Submitted March 19, 1975, revised June 20, 1975.

Reprint requests to: J. M. Stubblebine, MD, Ross Valley Medical Clinic, 1350 South Eliseo Drive, Greenbrae, CA 94904.

surgical procedures. Even though the system is very large, very complex and very important, the challenge is clear and unavoidable. We should not be overwhelmed or fearful; we must be both creative and courageous.

The economic pressures on the governor, and in fact on all of government, are both great and real—and of course must be weighed. Those of us outside of government administration must also bear them in mind and try to be sympathetic to the problems faced by Governor Brown. But we should just as clearly let him know we are opposed to waste and inefficiency in the use of our monies. I would also hope and pray we let him know that we understand the folly of providing less than good quality health care to anyone; that is surely the greatest, the most costly waste of all. But the governor, like all citizens, is caught in the vise of recession and increasing demands for services, with the strong arm of inflation tightening the vise. However, lamentations do no good; only basic, specific and major changes will help.

First, an issue of critical importance must be resolved, and on that depends all else. Does California want a double standard of health care; does California want two parallel systems of personal health delivery? If the answer is yes, little action is needed; if the answer is no, there is much to be done. However, both the medical profession and government have traditionally rejected the double standard as bad medicine, as being penny wise and pound foolish. Since the opening paragraphs of Title XIX of the Social Security Act (Sect. 1902 [10] [A] [ii]) states that all United States citizens have an equal right to health care, we must again reject the discriminatory separate system for the aged, the poor, the disabled, the blind, the mentally ill, the mentally retarded, the medically indigent, the prisoners. The alternative stated in the law is that of strengthening the present private system of health delivery as the only way to guarantee the same quality and kind of services equally to all.

The primary purpose in making these suggestions for major change is to improve health benefits available to anyone in need. Second, I am convinced that the publicly funded sector of personal health services can be made more effective (greater patient benefits to cost ratio). And third, I believe that the profession of medicine can lead the way in developing new attitudes by government and about government. My background is probably unique in California in that I can speak from the viewpoint of several years in the private practice of medicine as well as several years of public executive management in health. While these views are entirely my own responsibility, perhaps they can be acceptable to both government and medicine—and serve as a starting point to debate and to progress.

In order to change cost-benefit ratios, one thinks first of raising or lowering one or the other, but I propose neither. Instead I propose a shift of monies from unnecessary or duplicative bureaucracy to the purchase of the full range of clinical services. The major way savings in the delivery system are to be found is in improved, streamlined administration and in expanded availability of quality clinical services. California already provides the most generous benefits of any state under its medical assistance plan, but a few specific benefits should be expanded (such as teeth and hearing aids for the elderly and home health services). In any event, benefits should not be reduced; so we are forced to look at the way in which administrative and some program monies should be shifted. In order to do this, obstructive administration must be recognized for what it is; it must be replaced with simplified but auditable procedures that neither prevent health services nor penalize providers.

Recommendations

I

The first suggestion, said succinctly, is: consolidate and computerize. A single contract between the State and a single fiscal intermediary should be developed at once. This intermediary would provide fully computerized data systems for the management of all monies now going into duplicative systems. These separate systems presently are Blue Cross-Blue Shield (the Blues), California Dental Services (CDS) and the state-operated Short-Doyle (S-D) system. They should all be merged into a single intermediary program. Also to be included in the new system would be eligibility data, sent directly from the county level to the intermediary. All institutional providers, including home health agencies, should also be included in the single fiscal intermediary operation.

The direct linkage between county and intermediary would permit many efficiencies such as (1) reduction of personnel in Department of Health; (2) far quicker acquisition and verification of eligibility information; (3) computer

scanning for duplicated cases; (4) elimination of the sticky label system of utilization control. This last efficiency will allow two major improvements, in addition to the other efficiencies: (a) remove a major source of provider dissatisfaction, and (b) be consistent with anticipated national health insurance legislation. Present law establishes the Professional Standards Review Organization (PSRO) system, which is more and more moving toward "front end" controls, that is, utilization review in advance of services. This was the intent of the proof of eligibility (POE) stickers and the treatment authorization request (TAR) systems—and while they were generally effective, they did create resistances and animosities. The system suggested here should have much better provider approval and still be consistent with present and future federal legislation.

Yet other major advantages of this suggestion are in purely administrative savings. The fiscal intermediary could verify many claims that are now returned to the provider for time consuming reprocessing. In fact, the entire claim form could be simplified, thereby reducing the work load of the provider and staff. Another major benefit would be the relative ease of providing costs per patient by category of patient (such as number of dollars spent per Aid to Dependent Children patient or blind patient). This would then allow for the first time cost figures based on known, verifiable and comparable experience to be used in both budget preparations and rate setting for Prepaid Health Plans (PHP's) or Health Maintenance Organizations (HMO's).

Parenthetically the PHP's have received excessive negative attention; even their detractors generally come around to endorsing their basic concept. In so doing the persistent pressure needed for change gets displaced from administrative flaws to generalities. The PHP's could be vastly improved if only one additional fact were recognized—the major defect of many publicly funded personal health programs. There is a time-honored dictum in the field of public health—the dollars and services must be relatively higher in areas of greater need. It seems self-evident that this must be so if the level of health in areas of need is to be brought up to standard. If this concept prevailed, a few simple administrative changes could be made to remove most if not all of the grounds for criticism. These are (1) pay enrollers like insurance salesmen—that is, the longer an enrollee stays in the plan, the greater percentage of the enrollment fee is paid; (2) allow physicians an enrollment fee but allow it to be justified as health counseling and education; (3) increase cost allowances for greater percentage of a provider's case load being Medi-Cal patients and especially for being medically indigent patients. (The second suggestion makes use of the most powerful manpower resource, and the third creates a fiscal incentive to care for the most ill.)

This whole system would make full use of cathode ray tube (CRT) remote stations, a system I have described for years as the "United Air Lines system," though all major air lines have similar abilities. United, America's largest, has one computer to handle *all* of its passenger reservations, each with a great many bits of information, some of it held for months at a time. Also they have one or more remote CRT's at every airport and ticket counter. If the airlines can do it nationwide and save or make money, why should not the State of California do the same and reap the same benefits?

It makes little sense from the State or taxpayer's point of view to have competing systems such as the Blues and CDS. The latter organization deserves to be separate from that of the physicians, but the State should not allow a parochial attitude to justify spending millions of tax dollars. It is true the CDS contract is highly significant as a prepaid plan, but this feature can be retained while having the mechanical fiscal disbursement done elsewhere with similar functions. Exactly the same logic can be applied to the S-D program, but there other changes will be needed and will be discussed below.

The dollars available from these changes, to be shunted into direct clinical services, would be between $30 and $40 million per year out of $141.6 million for administration for fiscal year 1975-1976. The reductions or elimination of many functions presently done by the Department of Health and the Department of Benefit Payments would allow the transfer of many employees to clinical functions within several State departments such as Health, Youth Authority, Corrections. It would also allow many trained employees to work in other much needed areas—beautification, water and air pollution control, public safety, reforestation, and the like. Within the Department of Health and the Department of Benefit Payments, there would need to be an upgrading of many positions so as to meet an increased need for clinical and fiscal audit teams.

II

The second change can also be succinct: Pay now; audit later. One of the most intense dissatisfactions with the Medi-Cal program from both individual persons and institutions is delay in payment of a claim. Since the majority of claims of individual providers are paid relatively promptly, the same should be done with all claims, whether from individual persons or institutions. Reconciliation of audits can only be done after the fact; so why not pay at once and get an earlier start on auditing? This would also solve many facilities' cash flow difficulties, a major problem. As it is now, many hospitals and other facilities must borrow money at high short-term interest rates (10 to 13 percent) against accounts receivable. This interest then gets added to costs which are passed on to all payers, including Medi-Cal. And worst of all, neither patient nor hospital gets any benefit from this passing on of costs, and the hospital must also add on the clerical cost of keeping track of the accounts, the loans and the interest. If claims were paid on presentation and Medi-Cal accounts receivable could not be used as collateral for borrowing, the State could reduce total program costs by as much as $48 million per year in interest savings alone.

This change allowing more money to be spent on clinical services would have little or no effect on personnel needs of State departments. The only effect would be on the lending companies. While that may be regrettable, the State must give first consideration to stretching its health dollars. But the pay-on-demand policy would keep many dollars circulating, thereby benefiting all segments of the business community.

The present intermediary operation (the Blues) has the capability of providing periodic computer printouts of all payments to any provider. These should be done routinely and should be designed to provide all data to make such reports useful for both income tax and national health insurance purposes. Each provider could easily be given a quarterly *itemized* listing of claims paid, making subsequent audits much easier than the present quarterly report of total payments. It would also be an easy and potentially advisable thing to have each patient sign each claim form before submission. This would educate patients as to costs and procedures done and would also serve as a receipt for services rendered.

III

In collaboration with appropriate professional associations, the State should define levels of care within acute general hospitals for which the State will pay. These levels should be defined in terms of personnel who render services to patients—for example, the number of hours of nursing care per patient per day. Nursing care would include all personnel of the nursing service who are necessary to provide patient care. Similarly the other professional services should be defined with patients in mind rather than from an administrative point of view. One of the most rapidly rising costs in the health industry has been hospital costs, and these increases have been mostly due to personnel costs. If hospital management costs are to be controlled, personnel needs must be defined and limited. While this suggestion has the greatest potential savings, it is the most difficult to quantify. If actual savings cannot be realized, at least maintaining the level of costs for inpatient services in general hospitals is not too much to expect. It would move in the direction of determining institutional payments on the same basis as outpatient payments—that is, what was done directly on behalf of the patient.

IV

The State should abandon its discriminatory practices against health professions; follow the federal law in Title XIX and pay usual, customary and reasonable (UCR) medical charges. This would of course increase the expenditures in all areas of professional services, but it would make the medical system an economically honest system. It would make for much greater reliability of projections since they could be tied more closely to widely used indices. In this way forecasting and budgeting would be much more open and public, as well as reliable. As an example, physicians now are being paid at about 62 percent of what usual and customary fees were in 1968, but the determination of this schedule has not in the past been done publicly.

Pharmacists are similarly penalized by the same attitude toward costs. They are also hurt by the slowness of the State to ascertain wholesale costs on which are based allowable charges per prescription. Other professionals are similarly expected to accept cut-rate fees; home health services may be the object of the greatest discrimina-

tion. To the extent that this is true, it is wasteful of money, health and manpower—and is a particular hardship for the elderly.

In general the savings in dollars alone from the suggestions so far would *not* be immediately equal to the increases needed if UCR were adopted. But the State would benefit in a way more valuable and derive greater long-range benefits in two ways. First is the openly direct administrative system referred to above, and second is the single health delivery system. The double standard is far too costly in the long run because it allows, if not encourages, the most expensive category of patient—the medically indigent. Experience has shown these patients to have the least eligibility and an average cost per illness several times that of the person with greater eligibility. It is health poverty that drives costs up, and given time, our double standard approach will break our medical-dollar bank more surely than spending money for good treatment for all.

My last suggestion may be the most surprising but is most consistent with advocacy of eliminating the double standard: Phase out and eliminate Short-Doyle (S-D) in favor of the private systems. It should not be surprising, however, in view of the fact that many counties have for years relied partly on private practitioners as individual practitioners or as groups. Los Angeles County led the way, followed by Marin County and finally by many Valley counties that contract with the Kingsview complex. The Kingsview group has done an excellent job of providing a full range of services at reasonable costs and has at the same time been quickly responsive to counties' emerging needs for services. I would propose that all direct clinical services be transferred to the private sector and the indirect or educational consultative services be transferred to county health or education departments.

The assumption of all patient treatment services by the private sector would create new patterns of care. These would probably include: (1) Many patients would be followed through their mental disorder by their primary care physician; (2) mental health specialists would do more consultations with primary physicians; (3) specialists would employ more, or work more closely with, ancillary personnel such as social workers or psychologists or both; (4) private hospitals and day centers could expand; (5) new guidelines for independent professional activities by psychologists and social workers would need to be drawn up; (6) more outpatient group work would be done; (7) State hospitals would be more useful as back-up to the private sector and would be in much closer touch with the private sector; (8) only bona fide mental illness would be treated.

The benefits to the State are both clinical and fiscal—better treatment, or at least as good, and monetary savings. The dollar savings would come from the shift to fee for service, thus providing strongly positive motivation to actually treat patients. The improved treatment services would highlight the areas of failure of the present S-D system (such as for children and the aged). The S-D system has evolved into one dealing mostly with emancipated minors and young adults, and while many of them do need treatment, the needs of children and the elderly are more acute, and the S-D system was originally designed to give the elderly comprehensive care, including mental health care. The shift to the private sector would allow all ages to receive benefits more nearly according to need. It is most regrettable that despite the promises of many Social Security and health programs over the past forty years, the elderly are still badly underserved.

The abolition of S-D would eliminate the largest societal expression of the double standard in health. Is California ready for this kind of change? I would say it is—with certain understandings and with certain conditions applied. Virtually all mental health professionals are trained in hospitals and so know how to handle patients who need inpatient care; also psychoactive drugs have revolutionized psychiatric treatment. Control and sometimes cure of mental disorder is now possible, and public danger can be reduced. Because danger cannot be eliminated, however, the private sector must have easy access to security inpatient facilities.

If reasonable controls were imposed on mental health services in the private sector, savings could amount to one quarter of the current budget for nonhospital services, or about $60 million per year. These controls would include treatment only for diagnosable mental disorder (that is, no psychiatric treatment would be included for persons only disabled by physical disease or by educational, social or vocational handicap). For many mental health diagnoses, profiles would be developed, and treatment outside of such norms could easily be audited by clinical teams, as has been done for physical disorders. Individual provider profiles

would also be more extensively developed. Both kinds of profiles are being required by federal law to be done by PSRO's.

Discussion

How would such bold suggestions be implemented; what would the costs be; and most importantly, what would be the long-range benefits? Implementation could be done by combined executive-legislative action, but any such changes are bound to founder on opposition from public and professions alike unless there is much open discussion. Goal-oriented, time-limited and broad-based membership of gubernatorially appointed task forces would reduce these problems and give the State valuable input from both providers and consumers. It appears that both government and medicine are in communication already, but the public must also be brought in. The costs of initiating the changes recommended here would be negative (that is, there would be savings, but these should be shifted over to purchase of the full range of clinical services).

In order to know better how to spend the monies, it would help to see where they have come from and the changes year by year. Careful examination of Table 1 shows these changes, and especially the pronounced rate of growth of State government administration (the data in this table are from governors' annual budgets). The table also clearly shows how very much the professional services have failed to keep up with increase in either program costs or administration. Even when one takes only the last five years (1970 through 1975) so as to make allowance for start-up costs, the trends are the same. Another reason for comparing data before and after 1971 is that the Medi-Cal Reform Plan was begun on October 1, 1971. No matter how the data are examined, administrative or government costs are rising much the fastest, and professional services are rising the slowest. It is no wonder, then, that professionals (physicians, dentists, pharmacists, home health specialists) are crying foul. As if that were not enough, Governor Brown's first budget has recommended an increase in professional services of only 1.7 percent in the face of a projected inflation of 12.2 percent—but an 8.5 percent increase in nonprofessional salaries for State workers.

One of the unfortunate and probably undesired effects of the present out-of-balance budgeting is the creation of the double standard system —one for the poor and one for the average or well-to-do. In 1971-1972, while I was still Director of Health, it was common though quiet knowledge that only 64 percent of all practicing physicians were satisfied with their participation in the Medi-Cal program. Because the number was even then trending down and because of uncorrected dissatisfactions, I am sure that figure is now about 55 percent and in another year will be about 35 percent. Unless changes similar to those presented here are put into effect, the number of available professionals will continue to dwindle; they feel as if they are being subjected to double taxation—direct taxes and subventing the Medi-Cal program. Both the system and the health of the poor must be saved and saved now. There is no imperative more calculated to pay large long-range dividends. The changes advised here will reverse these manpower trends and return us to a

TABLE 1.—*Changes from Year to Year in State Costs Related to Medi-Cal*

	Annual Inflation Rate (percent)*	*California Medi-Cal Total Program (millions†)*	*California Medi-Cal Population (millions)*	*California Government Administrative Costs (millions†)*	*California Professional Services (millions‡)*
1966-67	2.7	$ 507.5	1.2982	$ 21.0	$143.3
1967-68	4.3	563.4	1.4757	28.1	145.4
1968-69	5.5	754.8	1.6436	36.6	186.0
1969-70	6.0	869.3	1.8569	36.4	212.0
1970-71	4.4	1,039.9	2.3777	60.3	260.7
1971-72	3.0	1,551.9	2.4126	75.1	284.6
1972-73	5.7	1,575.1	2.3139	97.5	329.4
1973-74	11.5	1,628.9	2.2396	125.6	396.6
1974-75§	15.0	2,042.1	2.4152	122.3	423.0
1975-76§	12.2	2,261.8	2.6297	141.6	430.3
Percent increase 1966-76		364	103	574	200
Percent increase 1970-76		118	10.6	135	65

*Bureau of Labor Statistics, nationwide.
†Includes federal, state and county monies.
‡Medical and dental services.
§Estimated.

single standard system, a costly system, but one much less costly than the one toward which we are heading. The various professional associations should, if necessary to prevent the creation of the double standard system and in order to protect the rights of the poor, join together and bring suit, forcing the State of California to obey the federal law. The professions must recognize such suits are system directed, not personally directed, and can be carried forward in a style and manner entirely respectful to both government and medicine. The professions should after all be the leaders in bringing about the best health for the most people, and that is the single standard system.

The most fundamental changes needed and recommended are ones of attitude: Government and medicine must trust each other to deal fairly and openly with each other and must actually do so. Both professions are in fact about 95 percent honest; the 5 percent can easily be identified and removed. In medicine and especially the Medi-Cal program that winnowing should be very easily done with computerized physician and disease profile data and active clinical audit teams. These latter functions can in the near future be taken over by the PSRO's and/or county medical societies or dental societies. With the medical profession being mostly honest and dishonesty easily controlled, the legislature and the governor should find it easy to supervise the contract with a single fiscal intermediary, to simplify accounting and managerial procedures and to put more money where it will produce more direct patient benefit. By the same token, the medical profession must recognize politicians really want to do what is best for all the people, but medicine must present hard data to back up its positions.

Most of all, the medical profession must recognize that the conservative approach is probably best in the consulting room but should be abandoned in the social-political area. Instead we should exercise our creativity in these areas and prove our imaginative and constructive capabilities. In this way government and medicine together should strive not to build complex systems with multiple denigrating checks and balances. What should be built is a single, simplified, auditable, inexpensive administrative system good for patients, providers and public alike.

The principles I am advocating are all to be found in a true story about a young, ambitious junior executive with the mail order division of a large retail store. When he noticed two complaints in a week from customers who paid for bicycles but did not receive them, he devised a systems analysis protocol. When he presented his proposal to an executive staff meeting, the conversation between him and the vice-president went like this:

V.P.: "How much will your analysis cost?"
Jr. Exec.: "$60,000."
V.P.: "How many complaints in a year do we get?"
Jr. Exec.: "Two or three."
V.P.: "How much does a bicycle cost us?"
Jr. Exec.: "$38."
V.P.: "After this, when anyone complains that they haven't received their bicycle, send them a bicycle."

Neither this story nor these suggestions contain all the wisdom or changes to make a perfect Medi-Cal system. There are undoubtedly many other refinements and improvements that could be developed and tested with good results. It was only my intent to show the order of magnitude of the approach needed and most of all the new attitudes needed.

Summary

Major changes in the Medi-Cal Program (in California the Title XIX or MedicAid Program) are needed now. They should include simplification, unification and computerization of many administrative functions, especially fiscal disbursement. The system should be made honest and law-abiding by adopting usual, customary and reasonable fee schedules, but furnishing each provider a quarterly itemized report of payments made. This report would have both audit and income tax benefits and usefulness. The changes recommended would generate about $150,000,000 in fiscal year 1975-1976 that should be shifted to purchase of clinical health services. The changes will require much cooperation among government, medicine and the general public. Professional organizations are urged to give serious consideration to joining forces in a suit against the State to force compliance with federal laws.

Refer to: Crowder JE: Financing undergraduate medical education (Medical Education). West J Med 123:247-249, Sep 1975

Financing Undergraduate Medical Education

JOHN E. CROWDER, MD, MS Educ, *Orange, California*

THE FINANCING of undergraduate medical education is an increasingly complex task. With such complexity come problems which do not respond to yesterday's solutions. This paper will review selected current problems in the financing of undergraduate medical education, and will analyze some innovative remedies being proposed to meet these financial difficulties.

Historical Perspective

Several developments occurring in recent years illustrate the growth of medical education in the United States. The medical schools' educational responsibility has increased from 65,000 (medical student equivalents) in 1961 to 110,000 in 1972. In 1961 undergraduate medical students accounted for approximately half of a student population of 65,000. This contrasts with 1972 when only 40 percent of medical students were medical undergraduates, the remainder being interns, residents, predoctoral and postdoctoral students in the basic and clinical sciences and some students in related health professions.[1]

Another indicator of change in medical education is the fact that university medical centers and affiliates accounted in 1970 for 20 percent of all the health care provided by the nation's hospitals compared with less than 14 percent in 1965.[1]

Expenditures for medical school operating programs grew from $200 million in 1961 to $780 million in 1971. At the same time, money spent for specifically sponsored research programs increased from $220 million to $930 million.[1]

Believing that the nation's medical schools contribute generally to the well-being of society, the federal government has gradually increased its support from less than $10 million in 1950 to more than $400 million in 1972.[1]

In 1972, a total of 45 state governments paid $332.6 million to partially support 105 public and private medical schools. One year later (1973) the amount of state government support increased to $400.7 million.[2] During the past 10 years available figures indicate that the states' proportional contribution to the operating expenditures of publicly-owned medical schools has remained constant at 55 percent.[3]

Whereas tuition and fees paid for 13 percent of the schools' total operating programs expenditures in the fiscal year 1960-1961, by 1971-1972 tuition and fees paid for only 8.9 percent of expenses. On the other hand professional fee income support increased from 6.0 percent in 1960-1961 to 16.3 percent in 1971-1972. Endowments and gifts accounted for 12.0 percent in 1960-1961 but had dropped to 8.1 percent by 1971-1972.[3]

The Problems

Emerging from the above statistics is a clear picture of increasing federal government financing of medical education in the face of static support from the state governments and declining

Dr. Crowder is Chief, Adult Inpatient and Emergency Psychiatric Service, Orange County Medical Center; and Assistant Adjunct Professor of Psychiatry and Human Behavior, University of California, Irvine, California College of Medicine.

Reprint requests to: J. E. Crowder, MD, Department of Psychiatry and Human Behavior, Orange County Medical Center, 101 City Drive South, Bldg. 2, Orange, CA 92668.

contributions proportionally from the private sector.

It is precisely this shift from private and local financing toward federal government support which is at the heart of the current problems. While it is expected that those giving financial support should receive a detailed accounting of how such funds are expended, the federal government is attaching more and more strings to its share of the funds. No longer is it willing to be merely a passive contributor; now it actively seeks to shape both educational and fiscal policies in the nation's medical schools. Where the government's goals coincide with the objectives of the medical schools, there is no conflict. But this is not always the case.

Compare the schools' reluctance to increase enrollment (fearing to overburden educational resources and anticipating a sacrifice in quality) with the desire by the federal government to link subsidies to enrollment boosts. The House Committee on Interstate and Foreign Commerce reviewed the nation's medical manpower needs and heard testimony offered by representatives of medical schools. The committee reported that it had "weighed carefully the proposal of the Administration, the Association of American Medical Colleges, and others testifying before the subcommittee not to include an expansion of enrollment requirement as a condition for receipt of capitation grants. Although the proposal might have merit if only small amounts of federal assistance were involved, the committee feels strongly that if schools are to receive assistance of the magnitude proposed in this bill there should be results—there should be increased manpower. The capitation grants will give the schools hundreds of thousands of dollars and in some cases millions of flexible funds to be used at their own discretion to meet their educational needs."[3]

The president of the Association of American Medical Colleges (AAMC), John A. D. Cooper, MD, recognizes that medical schools are in a precarious position and has cautioned the federal government against trying to find hasty, inadequate solutions: "The medical schools and their teaching hospitals which have become increasingly dependent on federal funds as their other fiscal resources become less adequate to carry out their socially vital missions, are being used as a convenient handle to advance the federal government's solutions to perceived shortcomings on the national health scene."[4]

According to the AAMC the annual cost per medical student of the educational program leading to the MD degree is estimated to range from $16,000 to $26,000 in 1972 dollars.[1]

Possible Solutions

Where will the money come from tomorrow?

In recommendations recently offered by the AAMC Committee on the Financing of Medical Education there is an emphasis on the search for multiple sources of support. The members recommended that the federal government should provide one third of the net cost of undergraduate medical education programs and should continue to offer grants and interest-subsidized loans to worthy students. State governments should continue their present level of support (about 55 percent) of public medical schools and should not overlook support for private schools either, to the extent that private schools contribute to the well-being of society. Only one short paragraph is devoted to general suggestions regarding a school's role in financing through solicitations of gifts and through fee-for-service income.[3]

The AAMC committee has not suggested anything new; rather, it has surveyed the national financial scene in medical education and has recommended continuation of the present direction. This is not adequate.

While its president bemoans the controls tied to federal subsidies, the AAMC through its Committee on the Financing of Medical Education has not found any viable alternatives.

Others have. Part of the solution lies in a largely untapped resource: the recipients of medical education—the physicians themselves.

Although physicians enjoy a generous lifestyle, high social standing and stable income, they do not at present pay for a major share of their education. It is true, of course, that physicians' income is subject to progressive federal and state income taxes to provide general revenues which in turn subsidize the medical schools. But does their obligation regarding the cost of their education stop here?

It has been estimated that the average physician will earn at least $1,500,000 in his productive lifetime. Yet, he currently is asked to pay a total of only $4,000 to $14,000 for his four years of medical education.[5]

In 1971-1972 the average student attending a private medical school in the United States paid tuition and fees accounting for 13.7 percent of the

costs of his education (down from 18.5 percent in 1960-1961). His counterpart at a public medical school paid tuition and fees accounting for only 4.7 percent of his medical education in 1971-1972 (down from 7.6 percent in 1960-1961).[3]

Perhaps medical students cannot afford to pay more than current tuition levels, but physicians certainly can.

Tuition and fees could be doubled or trebled without significantly affecting the applicant pool, *provided* that long-term loans are made available as described below.

Without loans, government subsidized or otherwise, only the children of very rich parents could pay the proposed $10,000 to $15,000 per year for a total of $40,000 to $60,000 in tuition and fees. Some may be frightened by the thought of incurring so large a debt. Yet the same young graduate thinks little about paying the same amount for a home encumbered with a 30 year mortgage. A young ophthalmologist who begins in solo practice may well have to borrow an equal amount to buy equipment and establish an office, to be repaid over 10 to 12 years.

Most of the currently available loans are scheduled to be repaid in full within 7 to 10 years after completion of postgraduate medical education. What is needed is the legal mechanism to be able to stretch out the repayment of larger loans over a longer period of time, such as 20 to 30 years.

This is by no means an original proposal. Daniel R. Challoner of the Institute of Medicine, Washington, D.C., proposed in January 1974 that income-contingent loans be established. Under his plan organizations such as medical schools or a government agency would lend the necessary funds to the student who would pledge to pay back a percentage of his gross income (based on the borrower's future income tax) for a period of years. Instead of simply paying off a fixed amount of principal plus interest, the borrower would continue to pay as long as he is working or until some predetermined maximum limit is achieved (such as 150 percent of the loan plus standard interest).[5]

Under Dr. Challoner's plan larger loans for higher tuition could be made allowing physicians from all income levels to pay for a greater share of their education. Such a proposal should have certain safeguards providing for limited or no liability if the borrower dies, is disabled or does not complete medical school.

A similar proposal was made regarding the support of physicians in graduate medical education by Herbert E. Kaufman of the University of Florida College of Medicine at Gainesville.[6]

"Mortgaging" one's self presents significant legal questions. What would be the security for repayment of the proposed loans? How could a prosperous physician be kept from avoiding repayment through bankruptcy proceedings? Would it be possible or desirable to link relicensure and continuing membership in medical societies with loan repayments? While these questions as well as other personal and ethical issues need to be resolved, the educational mortgage represents a viable alternative to increasing government aid with associated increasing control in medical education. It is a concept which deserves the support of the medical community and merits being the basis for a pilot research study. It is an idea whose time may have come.

REFERENCES

1. Committee on the Financing of Medical Education of the Association of American Medical Colleges: Undergraduate medical education: Elements, objectives, costs. J Med Educ 49:101-126, Jan 1974

2. Bromberg J: State roles in financing medical education (Datagram). J Med Educ 49:1193-1196, Dec 1974

3. Committee on the Financing of Medical Education of the Association of American Medical Colleges: Financing undergraduate medical education. J Med Educ 49:1091-1112, Nov 1974

4. Cooper JAD: Government control over the health sector (Editorial). J Med Educ 49:1192, Dec 1974

5. Challoner DR: The medical student pays for his education—Income contingent loans. N Engl J Med 290:160-162, Jan 17, 1974

6. Kaufman HE: Financing medical education (Communications). J Med Educ 49:897-899, Sep 1974

Refer to: Jones MW, Hamburger B: Physician supply in California, December 1973 (Socioeconomic Report of the Bureau of Research and Planning, California Medical Association). West J Med 123:250-253, Sep 1975

Physician Supply in California

MICHAEL W. JONES, MBA *and* BETTE HAMBURGER, BA, *San Francisco*

A Socioeconomic Report of the Bureau of Research and Planning
California Medical Association

As of December 31, 1973, there were 38,749 active non-federal physicians in California, or a ratio of 185.9 physicians to every 100,000 persons.

Both the number of physicians and the physician-population ratio have increased during the past several years. However, recent trends continue to indicate a greater concentration of physicians in metropolitan areas and fewer physicians located in isolated rural areas. Furthermore, although primary care specialists accounted for 45.8 percent of all physicians active in patient care, there has been no significant increase in this proportion during recent years despite efforts to augment the supply.

Figures relating to the distribution of physicians throughout California are presented in this report according to several geographic measures, and additional information is provided by specialty and type of activity. The most current data represent December 31, 1973 and certain data selected from earlier years are presented for comparative purposes.

Physician Figures Shown by County, PSRO Area

Data on physician distribution in California for 1973 are presented in Table 1, according to county and Professional Standards Review Organization (PSRO) area. The latter figures are presented here to provide for the grouping of counties into service areas as they have been designated by the federal government.*

The largest number of active physicians in California (excluding those employed by the federal government) was in Los Angeles County, where a total of 14,346 physicians represented 37 percent of all such physicians in the state. The Los Angeles County physician-population ratio was also well above average for the State, with 206.7 physicians per 100,000 persons, compared to the statewide ratio of 185.9. Other counties, however, have attracted comparatively greater concentrations of physicians. By far the highest ratio was in San Francisco County, where 3,587 physicians represented a ratio of 530.9 per 100,000 residents. It should be noted, however, that San Francisco and other counties in which a medical school is located have unusually high ratios due in part to this single factor.

Physicians Shortages Continue in Rural Counties

The only California county with no physicians in 1973 was Alpine, with a population of 650 persons. The lowest physician-population ratio, aside from Alpine, was in Modoc County, where two physicians serving 8,475 persons represented a ratio of 23.6 per 100,000. The relatively iso-

Mr. Jones is Director of the Division of Research and Socioeconomics, California Medical Association; Ms. Hamburger is a Research Assistant and Staff Coordinator.

Reprint requests to: Bureau of Research and Planning, California Medical Association, 731 Market Street, San Francisco, CA 94103.

*Professional Standards Review Organizations (PSRO) have been required in each state by law (P.L. 92-603, Social Security Amendments of 1972) to monitor federally financed health care services. Geographic areas, within which each PSRO will operate, were designated by the Department of Health, Education, and Welfare on January 1, 1974. Each PSRO area was chosen on the basis of compatible geographic, demographic and historical data. In California, twenty-eight areas were designated (listed in Table 1).

TABLE 1.—*Active Physicians (Non-Federal Government), Population and Physician-Population Ratios in California, by PSRO Area and County, December 31, 1973*

PSRO Area and County	*Active Non-Fed. Physicians*	*Civilian Population*	*Ratio (per 100,000)*
1. Del Norte	8	15,700	51.0
Humbolt	128	102,800	124.5
Lake	17	22,950	74.1
Mendocino	77	54,200	142.1
Sonoma	342	235,100	145.5
Total	572	430,750	132.8
2. Butte	160	114,300	140.0
Colusa	12	12,450	96.4
Glenn	10	18,350	54.5
Lassen	21	17,750	118.3
Modoc	2	8,475	23.6
Plumas	13	13,500	96.3
Shasta	124	86,000	144.2
Sierra	2	2,720	73.5
Siskiyou	28	35,200	79.5
Sutter	45	44,900	100.2
Tehama	22	31,650	69.5
Trinity	5	8,925	56.0
Yuba	49	44,750	109.5
Total	493	438,970	112.3
3. Marin	667	215,500	309.5
Napa	220	87,100	252.6
Solano	171	181,900	94.0
Total	1,058	484,500	218.4
4. El Dorado	55	53,500	102.8
Nevada	35	31,000	112.9
Placer	109	89,400	121.9
Sacramento	1,191	682,100	174.6
Yolo	244	103,600	235.5
Total	1,634	959,600	170.3
5. San Francisco	3,587	675,600	530.9
6. San Mateo	1,006	571,100	176.2
7. Alameda	2,103	1,097,400	191.6
Contra Costa	847	590,100	143.5
Total	2,950	1,687,500	174.8
8. Alpine	0	650	..
Amador	14	14,350	97.6
Calaveras	17	15,350	110.7
San Joaquin	381	300,100	127.0
Tuolumne	28	26,100	107.3
Total	440	356,550	123.4
9. Santa Clara	2,504	1,167,000	214.6
10. Mariposa	8	7,175	111.5
Merced	78	117,500	66.4
Stanislaus	278	210,400	132.1
Total	364	335,075	108.6
11. Fresno	579	438,700	132.0
Madera	25	44,900	55.7
Total	604	483,600	124.9
12. Monterey	329	258,600	127.2
San Benito	8	19,500	41.0
Santa Cruz	208	143,500	144.9
Total	545	421,600	129.3
13. Kings	40	68,500	58.4
Tulare	193	201,900	95.6
Total	233	270,400	86.2
14. Kern	359	340,900	105.3
15. Inyo	21	17,150	122.4
Mono	4	7,025	56.9
San Bernardino	1,038	699,700	148.3
Total	1,063	723,875	146.8
16. San Luis Obispo	170	121,500	139.9
Santa Barbara	509	275,600	184.7
Total	679	397,100	171.0
17. Ventura	538	426,100	126.3
18-25. Los Angeles	14,346	6,941,000	206.7
26. Orange	2,455	1,646,300	149.1
27. Riverside	609	507,800	119.9
28. Imperial	51	80,600	63.3
San Diego	2,659	1,502,600	177.0
Total	2,710	1,583,200	171.2
CALIFORNIA TOTAL	38,749	20,848,520	185.9

TABLE 2.—*Active Physicians (Non-Federal Government), Population and Physician-Population Ratios in California, by Type of Area, December 1971 and December 1973*

	December 1971			*December 1973*			*Percent Change*	
*Type of Area**	*Physicians*	*Population (000)*	*Ratio (per 100,000)*	*Physicians*	*Population (000)*	*Ratio (per 100,000)*	*Physicians*	*Ratio*
Major Metropolitan	29,920	15,379.1	194.5	31,821	15,614.1	203.8	6.4%	4.8%
Other Metropolitan	4,803	3,504.3	137.1	5,250	3,629.6	144.6	9.3	5.5
Counties Adjacent to Metropolitan Areas	819	786.7	104.1	853	845.4	100.9	4.2	(3.1)
Isolated Semirural	686	609.6	112.5	724	637.4	113.6	5.5	1.0
Isolated Rural	101	114.5	88.2	101	122.0	82.8	..	(6.1)
State Total	36,329	20,394.2	178.1	38,749	20,848.5	185.9	6.7	4.3

*Counties included in each classification:

Major Metropolitan: Alameda, Contra Costa, Los Angeles, Marin, Orange, San Diego, San Francisco, San Mateo, Riverside, San Bernardino, Santa Clara.

Other Metropolitan: Fresno, Kern, Sacramento, San Joaquin, Santa Barbara, Monterey, Napa, Placer, Solano, Sonoma, Stanislaus, Ventura, Yolo.

Adjacent: Amador, Calaveras, El Dorado, Kings, Madera, Merced, San Benito, San Luis Obispo, Santa Cruz, Sutter, Tulare.

Isolated Semi-rural: Butte, Colusa, Glenn, Humboldt, Imperial, Mendocino, Nevada, Shasta, Siskiyou, Tehama, Tuolumne, Yuba.

Isolated Rural: Del Norte, Inyo, Lassen, Modoc, Alpine, Lake, Mariposa, Mono, Plumas, Sierra, Trinity.

TABLE 3.—*Physicians (Non-Federal Government) in California, by Specialty and Major Professional Activity, December 31, 1973*

		Major Professional Activity								
		Patient Care					Other Professional Activity			
				Hospital Based Practice						
Specialty	*Total Physicians*	*Total*	*Office Based Practice*	*Intern*	*Resident*	*Full Time Staff*	*Medical Teaching*	*Administration*	*Research*	*Other*
General Practice	6,629	6,510	6,092	..	198	220	10	66	14	29
Medical Specialties	9,633	8,685	6,531	482	1,210	462	224	275	400	49
Allergy	195	174	169	..	..	5	3	7	11	..
Cardiovascular diseases	722	627	568	..	..	59	23	14	55	3
Dermatology	609	579	527	..	45	7	12	7	9	2
Gastroenterology	194	167	151	..	..	16	12	4	11	..
Internal medicine	5,383	4,874	3,454	349	854	217	98	152	231	28
Pediatrics	2,189	1,998	1,458	133	299	108	52	72	52	15
Pediatric allergy	54	45	36	..	7	2	2	2	5	..
Pediatric cardiology	65	50	34	..	5	11	4	5	6	..
Pulmonary diseases	222	171	134	..	..	37	18	12	20	1
Surgical Specialties	10,203	9,867	8,289	176	1,181	221	122	107	83	24
General surgery	2,915	2,820	2,177	127	424	92	35	41	15	4
Neurological surgery	368	346	279	..	52	15	10	4	5	3
Obstetrics/Gynecology	2,297	2,211	1,879	49	245	38	29	25	28	4
Ophthalmology	1,211	1,169	1,060	..	96	13	14	9	15	4
Orthopedic surgery	1,467	1,431	1,225	..	185	21	16	10	7	3
Otolaryngology	623	607	545	..	56	6	5	5	4	2
Plastic surgery	302	290	255	..	30	5	4	1	5	2
Colon and rectal surgery	87	86	84	..	1	1	..	..	..	1
Thoracic surgery	206	198	165	..	21	12	3	3	2	..
Urology	727	709	620	..	71	18	6	9	2	1
Other Specialties	10,678	8,997	6,272	589	1,254	882	281	792	384	224
Aerospace medicine	37	21	18	..	2	1	1	6	6	3
Anesthesiology	1,655	1,561	1,352	..	153	56	62	13	14	5
Child psychiatry	317	256	192	..	46	18	16	33	8	4
Diagnostic radiology	403	364	246	..	84	34	18	8	4	9
Forensic pathology	29	13	10	..	3	..	1	2	..	13
Neurology	411	347	246	..	73	28	20	7	35	2
Occupational medicine	262	208	201	..	..	7	..	45	1	8
Psychiatry	2,877	2,537	1,826	..	406	305	45	220	52	23
Pathology	1,068	863	527	28	169	139	31	45	57	72
Physical medicine	138	117	85	..	8	24	3	13	..	5
General preventive medicine	95	42	35	..	5	2	6	37	8	2
Public health	355	127	114	..	8	5	13	179	18	18
Radiology	1,271	1,194	891	..	182	121	23	17	14	23
Thoracic surgery	154	144	100	..	34	10	4	3	3	..
Other specialty	750	399	301	..	..	98	30	138	154	29
Unspecified	856	804	128	561	81	34	8	26	10	8
Not Classified	1,606	..	..	..	..	..	..	..	..	..
Inactive	3,689	..	..	..	..	..	..	..	..	..
TOTAL PHYSICIANS	42,438	34,059	27,184	1,247	3,843	1,785	637	1,240	881	326

TABLE 4.—*Physicians in Primary Care and Patient Care, and Physician-Population Ratios, California, 1971 and 1973*

	Active Patient Care Physicians				Percent Change 1971 to 1973	
	Number		Ratio			
	1971	*1973*	*1971*	*1973*	*Number*	*Ratio*
General Practice	6,751	6,510	33.1	31.2	(3.6)%	(5.7)%
Internal Medicine	4,478	4,874	22.0	23.4	8.8	6.4
Pediatrics	1,943	1,998	9.5	9.6	2.8	1.1
Obstetrics/Gynecology	2,122	2,211	10.4	10.6	4.2	1.9
Total Primary Care MDs	15,294	15,593	75.0	74.8	2.0	(0.3)
Other Patient Care MDs	17,716	18,466	86.9	88.6	4.2	2.0
Total Patient Care MDs*	33,010	34,059	161.9	163.4	3.2	1.0

*Excludes physicians whose specialties are unknown.

lated nature of this county, as well as other low-ratio counties such as Del Norte, Trinity and Mono, clearly suggest the continuation of the problem of geographic maldistribution discussed more fully in 1973 in a *Socioeconomic Report* published by the California Medical Association.[1]

It should be noted here that ratios alone do not provide a reliable measure of medical manpower adequacy. The ratios provided in this report are intended for general comparative purposes only. Nevertheless, they can suggest discrepancies in levels of adequacy when the disparities among various areas are major.

Increased Ratios Shown in Most Areas

As might be expected, most active physicians were located in metropolitan areas. Table 2 details the distribution of California physicians according to several demographic categories for 1971 and 1973. In December 1973 metropolitan areas accounted for 95.7 percent of physicians, while rural areas accounted for just 2.1 percent.

From 1971 to 1973 the greatest percent increase in numbers of physicians was in metropolitan areas—a 6.4 percent increase in major metropolitan areas and a 9.3 percent increase in "other" metropolitan areas. While semirural areas increased 5.5 percent, the rural areas showed no change in physician numbers.

Comparison with population changes during these two years indicates that statewide, as well as in both metropolitan and semirural areas, the number of physicians increased by higher percentages than the population, while in counties adjacent to metropolitan areas and in rural areas the population increases were greater than physician increases. The most substantial relative increase was in "other" metropolitan areas, a listing of which may be found in the table.

The physician-population ratio decreased most dramatically—by 6.1 percent—in rural areas. This decrease brings the rural situation to a ratio of just 82.8 per 100,000 residents, compared with the 203.8 ratio in major metropolitan areas. This ratio is nevertheless higher than that recorded during the 1960's, and fluctuations of this nature are not unusual since the movement of one or two physicians or slight population changes result in a perceptible ratio change.

Further Declines in General Practice Shown

Table 3 contains information about specialty and major professional activity of California physicians, excluding those employed by the federal government. Over 80 percent of these physicians were primarily involved in patient care activities, including 27,184 physicians in office based practice and 6,875 interns, residents and full-time staff physicians in hospital based practices.

The largest single percentage of office based physicians (22.4 percent) was to be found in the field of general or family practice. Nevertheless, this proportion represents a continuation in the decline that has been evidenced during the past few decades.

Continuing Need for Primary Care Physicians

Data relating to primary care physicians (general practitioners, internists, pediatricians and obstetrician/gynecologists) for 1971 and 1973 are highlighted in Table 4. As noted previously, general practice was the only primary care specialty which experienced a decrease in numbers (241 physicians) from 1971 to 1973. The greatest increase among primary care physicians during this period was in internal medicine (396 physicians). It should be noted that figures in this table pertain only to physicians involved in *direct* patient care, and thus exclude administrators, teachers and researchers. The numbers and resultant ratios are, therefore, lower than those shown in Tables 1 and 2.

The rate of increase in primary care physicians in 1973 was below the rate of increase in other types of physicians and in the population. Thus, a slight decline in the ratio of primary care physicians to population, from 75.0 to 74.8 per 100,000, is shown. The apparent decline is difficult to evaluate in terms of the availability of primary care services, however, since the degree to which services are provided by physicians listed in other types of specialties or subspecialties cannot be determined.[2]

REFERENCES

1. Jones MW: Physician supply—An analysis of distribution in California. Socioeconomic Report, Bureau of Research and Planning, California Medical Association XIII:Feb 1973

2. Jones MW: Physician supply—An analysis of specialty distribution. Socioeconomic Report, Bureau of Research and Planning, California Medical Association XIII:March 1973

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CURRENT PEDIATRIC DIAGNOSIS AND TREATMENT—Third Edition—C. Henry Kempe, MD, Professor of Pediatrics, University of Colorado School of Medicine, Denver; Henry K. Silver, MD, Professor of Pediatrics, University of Colorado School of Medicine; Donough O'Brien, MD, Professor of Pediatrics, University of Colorado School of Medicine; and associate authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 1020 pages, $12.00.

That this is the third edition of this useful pediatric text is ample evidence of its excellent reception. It provides comprehensive coverage of virtually all facets of child care, and includes attention to ambulatory care procedures as well as chapters concerning all of the important categories of illnesses of children. Many of the latter are covered more completely than in earlier editions and virtually all have been updated substantially.

The concise style and the organization of the subject material facilitates the use of this text as an aid in differential diagnosis and lends itself well to rapid review of subject areas by the busy physician.

A series of chapters describing diagnostic and therapeutic procedures, fluid therapy, drug therapy, and antimicrobial drugs provides a useful source of information, particularly for the physician in training, as well as for those drugs or procedures used infrequently. A section on interpretation of biochemical values in infants and children, including various screening procedures, will be particularly useful.

This is an excellent outline of pediatrics, and a useful source of current authoritative references for additional reading. At its price it is perhaps the greatest bargain in books (or anything else, for that matter) today.

PAUL F. WEHRLE, MD

* * *

DIAGNOSTIC AND THERAPEUTIC AIDS IN UROLOGY—Henry Bodner, MD, Associate Clinical Professor, Department of Surgery (Urology), Loma Linda University School of Medicine, White Memorial Hospital Division, Los Angeles; In collaboration with John S. Arconti, Jr., MD, Formerly Clinical Instructor, Department of Surgery (Urology), UCLA Center for the Health Sciencs; Allan H. Howard, MD, Associate Clinical Professor, Department of Surgery (Urology), University of California Medical Center, Irvine; and Robert O. Pearman, MD, Associate Professor, Department of Surgery (Urology), UCLA Center for the Health Sciences, Los Angeles. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62703), 1974. 332 pages, $24.75.

This volume is a "meaty" compendium of practical urological information. It is an assemblage of facts, figures, suggestions and admonitions which represent the contributions of nearly two hundred experienced urologists from a wide geographic area. The Editor-in-Chief, Henry Bodner, MD, relates that most of the ideas came from the "Weekly Urological Clinical Letter" published by him since 1957. He and his editorial colleagues have extracted the most significant material, added ideas of their own and presented it here in a very well organized format.

In general the material was selected because it seems practical and bears some promise of permanent value—in so far as that term has any real meaning. They have added suggestions on the organization of the urologist's office. Most of this is good but relates chiefly to the beginner in private practice and in that reference the advice is good. Some qualifications arise here. The suggested basic equipment list is suitable for a very large office setup or even more so for those centers where a fully equipped outpatient urological service is provided. The list given is far too elaborate in my opinion for the average young practitioner in the field. I do not find the section on office business problems or management, as mentioned in the jacket "blurb," but this omission is just as well as being out of place here.

In general the chapter on armamentarium is thorough and well done. I thought that the following chapter, "The Urine and Related Factors," was excellent. Such things as the tables relating to urine colors and to drug implications are well presented and very useful. I was glad to see the information on urine flow and collection factors.

The remainder of the book presents a wealth of relevant information and suggestions (given as mentioned on the jacket) on the framework of the urologic system taking each structure in turn. There are times when the opinion of the editorial staff might seem somewhat prejudiced. Such an example is that referring to renal biopsy techniques.

I am most impressed with the usefulness of this volume. I find little if any room for real criticism. I recommend it for all practicing urologists.

THOMAS F. CONROY, JR., MD

* * *

ABDOMINAL OPERATIONS—Sixth Edition—Volumes 1 and 2—Rodney Maingot, FRCS, and British and American Contributors. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., Publishers, Englewood Cliffs, NJ (07632), 1974. 2240 pages, $82.50.

Dr. Maingot has been, for many years, a top British Statesman of Surgery and I have in my library the second, 1948, and the fourth, 1961, editions, the latter autographed to me when he was a delightful and impressive guest speaker at the Society of Graduate Surgeons of Los Angeles County, USC Medical Center Circa in 1963.

The present two volumes are well updated with chapters by a variety of authors who are tops in their specialties and would be valuable reading for both beginning and experienced surgeons and of excellent reference value for doctors in Internal Medicine, General Practice and even many other fields.

A particular value of many chapters is that while alternative procedures are presented, reasons are clearly stated why a procedure is or is not the operation of choice under various conditions.

Dr. Maingot has always seemed to me quite like Winston Churchill both in appearance and in manner and his personality and decisiveness come through the parts that he has prepared and one can almost see his extreme vigor and his typical British sense of humor even in scientific presentations.

The history and evolution of the various procedures is interestingly documented in most chapters so that one can settle down to an evening of informative reading or look up a quick but adequate reference when needed.

FRED M. ANDERSON, MD

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

September 22-26—**Medical Oncology Review.** American College of Physicians at Huntington Sheraton Hotel, Pasadena. Monday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, Pa. 19104.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** See Radiology and Pathology, September 27-28.

October 8—**Carcinoma of the Kidney, Adrenal, Retroperitoneum and Penis—3rd Annual Los Angeles Urological Cancer Conference.** L.A. Urological Society and American Cancer Society, Calif. Division, at Sheraton Hotel, Los Angeles Airport. Wednesday. Contact: William H. Tanner, ACS, 2932 Wilshire Blvd., Santa Monica 90403. (213) 828-7474.

November 7-8—**San Francisco Cancer Symposium of 1975—Current Concepts of Cancers Occurring in the Neck and in the Female Genital Tract.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center, San Francisco. $150. Friday-Saturday. Contact: Dept. of Cont. Ed., Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120.

November 14-15—**Breast Cancer: Its Impact on the Patient, Family and Community.** West Coast Cancer Foundation; Univ. of the Pacific, School of Medical Sciences; St. Mary's Hospital and Med. Ctr.; PMC, Dept. of Psychological & Social Medicine, at Hyatt Regency, San Francisco. Friday-Saturday. $75 if registered before Nov. 1; $90, late registration. Contact: Jerome M. Vaeth, MD, Dir., WCCF, 2340 Clay St., P.O. Box 7999, San Francisco 94120. (415) 563-5213.

November 22—**Practical Oncology.** UCD. Saturday.

December 7—**Seminar on Head and Neck Tumors—Semi-Annual.** California Tumor Tissue Registry, Hyatt Hotel, San Francisco. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

MEDICINE

September 17—**Cardiology I Symposium—1975.** DREW at Martin Luther King, Jr., Hospital, Los Angeles. Wednesday.

September 17—**Kidney Disease — 15th Annual Symposium.** Kidney Foundation of Southern California at Ambassador Hotel, Los Angeles. Wednesday. $30. Contact: Jack W. Coburn, MD, Kidney Foundation of So. Calif., 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18-June.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 18 hrs. $25.

September 21—**Hypertension.** Hawaii Medical Assn. and Hawaii Heart Assn. at Princess Kaiulani Hotel, Honolulu. Sunday. Contact: Mrs. Molly Austin, Hawaii Heart Assn., 245 N. Kukai St., Honolulu 96817.

September 26-27—**Infectious Disease—8th Annual Fall Meeting.** Children's Hospital of Oakland at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Calori, Medical Staff Office, Children's Hospital Medical Center, Oakland 94609. (415) 654-5600.

September 27—**Cardiovascular Disease—19th Annual Symposium.** American Heart Assn., Santa Barbara and San Luis Obispo Counties Chapter; Ventura County Heart Assn. at University Center, UC, Santa Barbara. Saturday. Contact: Judith Browning, Exec. Dir., AHA, Santa Barbara and San Luis Obispo Counties Chapter, P.O. Box 1071, San Luis Obispo 93406. (805) 544-1505.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

September 27-28—**Workshop in Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 1-3—**San Francisco Heart Association—45th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. 18 hrs. $50. Contact: Evelyn Berggren, San Francisco Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 1-4—**Laboratory Advance in Internal Medicine.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

October 2-4—**Endocrinology and Metabolism: Current Perspectives.** American College of Physicians at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: Ronald S. Swerdloff, MD, 21510 S. Main St., Carson 90745.

October 3—**Kidney Foundation of Northern California—Symposium.** Hyatt Union Square, San Francisco. Friday. Contact: Michael H. Humphreys, MD, Prog. Chr., Kidney Foundation of No. Calif., UC Renal Center, S. F. General Hospital, Bldg. 100, Rm., 350, San Francisco 94110.

October 3-4—**Cardiology Symposium.** Southern California Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley C. Gach, Coord., So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Rm. 6014, Los Angeles 90027. (213) 667-4241.

October 4—**Hypertension.** USC. Saturday.

October 4—**Gastroenteritis.** Childrens Hospital of Orange County, Orange. Saturday. Contact: Merl J. Carson, MD, Med. Dir., CHOC, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

October 8—**Newer Concepts in Hypertension.** West Hills Hospital, Canoga Park. Wednesday. Contact: Continuing Medical Education, West Hills Hospital, 7300 Medical Center Dr., Canoga Park 91307. (213) 884-7060.

October 9-12—**California Society of Internal Medicine.** Vacation Village, San Diego. Thursday-Sunday. Contact: Carol H. Handley, Exec. Dir., SCIM, 1412 Central Towers, 703 Market Street., San Francisco 94103. (415) 362-1548.

October 10-11—**Controversies in Congenital Heart Disease.** The Earl and Loraine Miller Children's Hospital Medical Center and Long Beach Heart Assn. at Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. $125. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 15-18—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Saturday.

October 15-19—**American Association for Clinical Immunology and Allergy.** Riviera Hotel, Palm Springs. Wednesday-Sunday. Contact: Howard Silber, AACIA, P.O. Box 912, DTS, Omaha, Neb. 68101. (402) 558-5345.

October 18-19—**Dermatologic Surgery.** See Surgery, October 18-19.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** See Of Interest To All, October 18-19.

October 24-25—**Symposium on Respiratory Care.** Fresno Community Hospital. Friday-Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

October 26-30—**American College of Chest Physicians—41st Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Thursday, Contact: Alfred Soffer, MD, Exec. Dir., ACCP, 911 Busse Highway, Park Ridge, Ill. 60068. (312) 698-2200.

November 10-14—**Pediatric Allergy and Clinical Immunology—11th Annual Workshop.** UCSF. Monday-Friday.

November 13—**Lung Association of Contra Costa and Solano Counties—Physicians' Postgraduate Course.** Sheraton Inn, Concord. Thursday. Contact: Pat Gilman, 105 Astrid Dr., Pleasant Hill 94523. (415) 935-0472.

November 15—**Pediatric Dermatology.** Childrens Hospital of Orange County, Orange. Saturday. Contact: Merl J. Carson, MD, Med. Dir., CHOC, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

November 16—**Heparin-Thrombosis Seminar.** American Heart Assn. Council on Thrombosis; American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Sunday. $30. Contact: Symposiums International, 130 El Camino Dr., Beverly Hills 90212. (213) 273-2157.

November 16—**Hypertension.** UCLA and Granada Hills Community Hospital at Calif. State University, Northridge. Sunday.

November 16-19—**Gastroenterology: Current Topics with Emphasis on Peptic Ulcer.** UCLA at Kona Kai Hotel, San Diego. Sunday-Wednesday.

November 17-21—**American Heart Association.** Disneyland Hotel, Anaheim. Monday-Friday. Contact: William W. Moore, Exec. V. P., AHA, 44 E. 23rd St., N.Y. 10010.

November 19-21—**Practical Electrocardiography—Chungs' Approach.** Memorial Hospital Medical Center, UCI Center for Health Education, Long Beach. Wednesday-Friday. $150. Contact: Donald K. Chung, MD, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 19-21—**Respiratory Failure.** USC. Friday-Sunday.

November 20-22—**West Coast Allergy Society.** Royal Inn at the Wharf, San Diego. Thursday-Saturday. Contact: Harvey O. Randel, MD, WCAS, 2164 SW Park Pl., Portland, Ore. 97205. (503) 226-1555.

November 22—**Nuclear Cardiology.** UCSF. Saturday.

December 4-6—**Rheumatic Diseases—4th Annual Western Regional Conference.** UCSF at Claremont Hotel, Oakland. Thursday-Saturday.

December 5-6—**Diabetes Mellitus.** STAN and Santa Clara County Diabetes Assn. at Rickey's Hyatt House, Palo Alto. Friday-Saturday. Contact: STAN.

December 6—**Advances in Diabetes Mellitus, Calcium and Water Disorders.** Daniel Freeman Memorial Hospital at International Hotel, Los Angeles. Saturday. $35. Contact: Joan Covell, Med. Staff Sec., Daniel Freeman Memorial Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 672-0112, ext. 206.

December 6—**The Asthmatic.** UCLA. Saturday.

December 6-11—**American Academy of Dermatology.** Hilton Hotel, San Francisco. Saturday-Thursday. Contact: Betty Suor, Exec. Dir., AAD, 1116 S. Fifth, Tacoma, Wa. 98405. (206) 572-4747.

December 7-9—**Advances in Heart Disease—1976.** American College of Cardiology at Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 10—**Colloquia in Cardiology—No. 8: Stress and the Heart—The Influence and Management of Stress in Heart Disease.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

MENTAL RETARDATION

October 30-31—**Mental Retardation.** USC. Thursday-Friday.

OBSTETRICS AND GYNECOLOGY

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

(Continued on Page 37)

(Continued from Page 34)

September 25—**Non-Traditional Sexually Transmitted Diseases.** See Of Interest To All, September 25.

September 25-27—**Fall Symposium in Obstetrics and Gynecology—Oncology, Endocrinology and Infertility.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Saturday.

September 27-October 4—**Workshops in Gynecologic Oncology, High Risk Pregnancy and Endocrinology-Infertility.** UCSF at Maui, Hawaii. One week.

October 4—**Office Gynecology.** PMC. Saturday.

October 5-10—**Pacific Coast Obstetrical and Gynecological Society.** Pebble Beach. Sunday-Friday. Contact: Melvin W. Breese, MD, 1133 SW Market St., Portland, Ore. 97201.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** See Of Interest To All, October 7-8.

October 8-10—**Fetal Monitoring.** USC. Wednesday-Friday.

October 13-14—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. $130. Contact: Ellen Woolfson, Cont. Ed. Coord., Harbor Gen. Hospital, 1124 W. Carson A-19, Torrance 90502. (213) 775-7711, ext. 1373.

October 15-19—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 31 hrs. $15 for members; $25, non-members. Contact: Ms. Dee Davis, Exec. Sec., PCFS, 5410 Wilshire Blvd., Suite 600, Los Angeles 90036. (213) 937-5514.

October 18—**Office Management of Common Gynecological Disorders.** Palo Alto Medical Clinic, Palo Alto. Saturday. Contact: William D. McKee, MD, Dept. of Allergy, Palo Alto Med. Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

October 20-24—**Ob/Gyn Review.** USC. Monday-Friday.

October 24-25—**Perinatal Neurology.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday.

October 31—**Advances in Gynecology.** Northern California Ob-Gyn Society at Sacramento. Friday. Contact: Solon Barbis, MD, 1816 Professional Dr., Sacramento 95825.

November 14-15—**Breast Cancer: Its Impact on the Patient, Family and Community.** See Cancer, November 14-15.

December 13-14—**Birth and Rebirth.** UC Extension, Santa Cruz. Saturday-Sunday. 15 hrs. $40. Contact: Darla Chadima, Cont. Ed. Specialist, UC Extension, Santa Cruz 95064. (408) 429-2971.

PEDIATRICS

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** See Surgery, September 18.

September 24-25—**Brennemann Memorial Lectures—32nd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eve Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 4—**Gastroenteritis.** See Medicine, October 4.

October 10-11—**Controversies in Congenital Heart Disease.** See Medicine, October 10-11.

October 13-14—**New Horizons in Perinatal Intensive Care.** See Obstetrics and Gynecology, October 13-14.

November 6-7—**Pediatric Dialysis.** USC. Thursday-Friday.

November 8—**Caregiving for Infants During the First Two Years of Life—2nd Annual Child Development Conference.** UCLA. Saturday.

November 10-14—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 10-14.

November 11-13—**Pediatric and Adolescent Aspects of Trauma.** USC at Gene Autry Hotel, Palm Springs. Tuesday-Thursday.

November 15—**Pediatric Dermatology.** See Medicine, November 15.

December 6—**American Academy of Pediatrics, California Chapter 1, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

PSYCHIATRY

September 20—**Psychotherapy.** UCD, Central California Psychiatric Society and Fresno County Dept. of Mental Health at Rodeway Inn, Fresno. Saturday. Contact: Central Calif. Psych. Society, 451 Parkfair Dr., Suite 4, Sacramento 95825. (916) 488-4320.

November 10-14—**Group Therapy Seminars.** UCSF at Leamington Hotel, Oakland. Monday-Friday.

RADIOLOGY AND PATHOLOGY

September 20—**Nuclear Medicine Symposium — Imaging the Head.** Nuclear Medicine Section of Memorial Hospital Association at Holiday Inn (1612 Dale Road, on U.S. 99), Modesto. Saturday. No fee. Contact: Darrell K. Oberg, MD, 600 Coffee Rd., Modesto 95355. (209) 524-1211.

September 27—**Current Topics in Diagnostic Radiology.** Southern California Permanente Medical Group at Marriott Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 27-28—**Nuclear Medicine.** UCLA. Saturday-Sunday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** UCLA. Saturday-Sunday.

October 8-12—**American Society of Therapeutic Radiologists.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Sheila McGing, Exec. Sec., ASTR, 20 N. Wacker Dr., Room 2920, Chicago, Ill. 60606.

October 20-24—**Pathology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

November 7-9—**Modern G. U. Radiology—The Practical Approach (9th Annual Leo G. Rigler Symposium).** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday.

December 3-7—**California Society of Pathologists—Annual Meeting.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Mr. Richard E. Hall, CSP, 1225 8th St., Suite 590, Sacramento 95814. (916) 446-6001.

December 12—**Principles and Procedures of Blood Gases.** PMC. Saturday. $65.

December 12-14—**Fluid and Electrolytes.** USC at Tennis Club, Palm Springs. Friday-Sunday.

SURGERY AND ANESTHESIOLOGY

September 18-June—**Review and Update in Surgery, Pediatrics, Ob-Gyn and Internal Medicine.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Thursday evenings. Contact: Linda Alperstein, Coordinator, Cont. Med. Ed., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

September 26-28—**Anesthesia and Cardiovascular Disease.** Anesthesiology Education Foundation and Calif. Society of Anesthesiologists at Holiday Inn, Monterey. Friday-Sunday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

September 27-28—**American Society of Anesthesiologists—Regional Refresher Course.** Disneyland Hotel, Anaheim. Saturday-Sunday. 8 hrs. $50. Contact: John S. Hattox, Jr., MD, ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

September 27-28—**Workshop in Dermatologic Surgery.** See Medicine, September 27-28.

September 28-October 1—**Western Neurosurgical Society.**

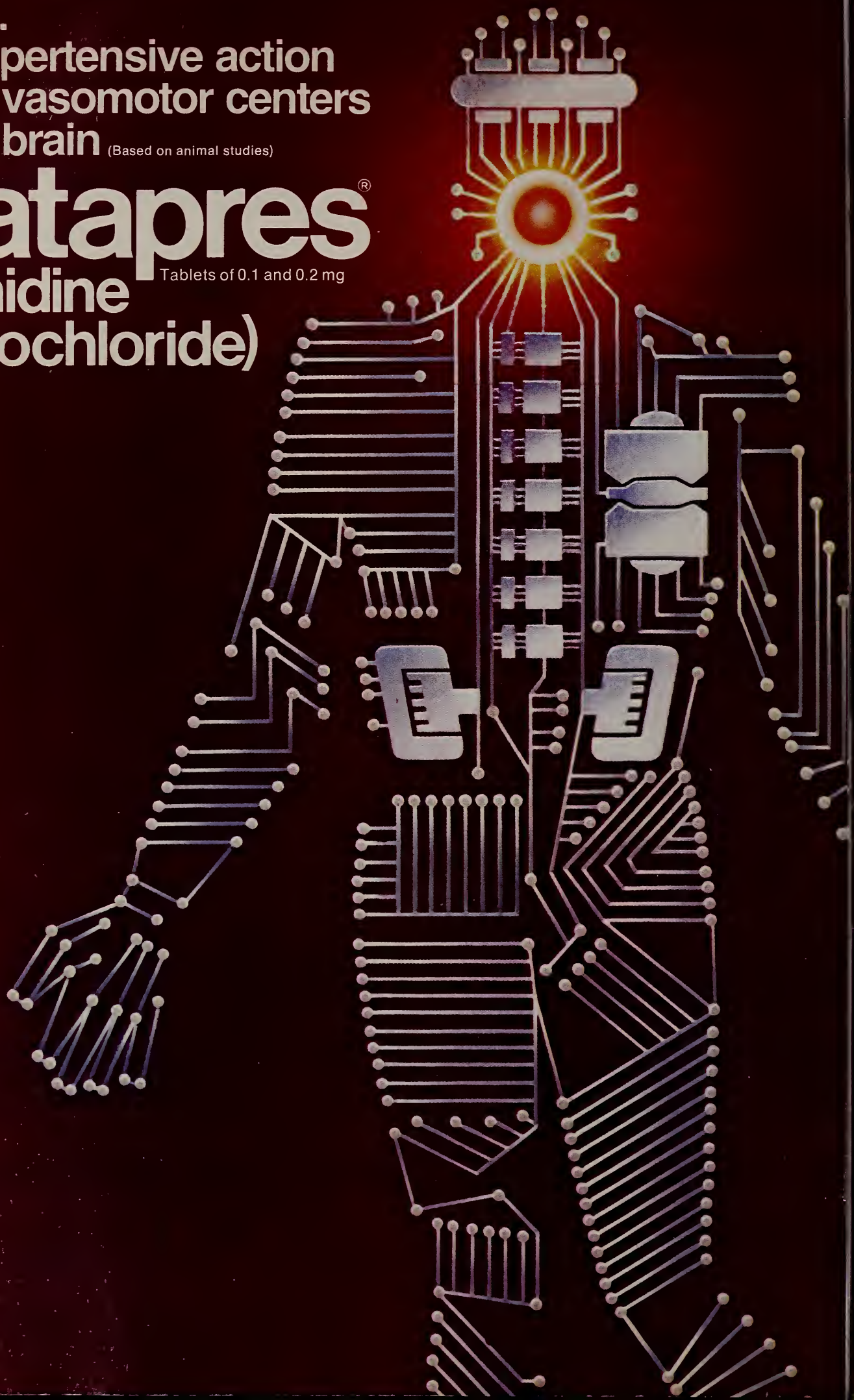
(Continued on Page 42)

Now...
antihypertensive action
at the vasomotor centers
in the brain (Based on animal studies)

Catapres®

Tablets of 0.1 and 0.2 mg

(clonidine
hydrochloride)



Bacterial proliferation in the urine is a function of time and retention, as the chart below indicates. Because each 1-Gm dose provides up to 12 hours' antibacterial activity, Gantanol protects the patient during the hours of sleep, when urinary retention favors bacterial buildup in the bladder. Counts of susceptible *E. coli* are usually reduced from 10^5/ml to sterile urine within 48 hours.

your patient sleeps

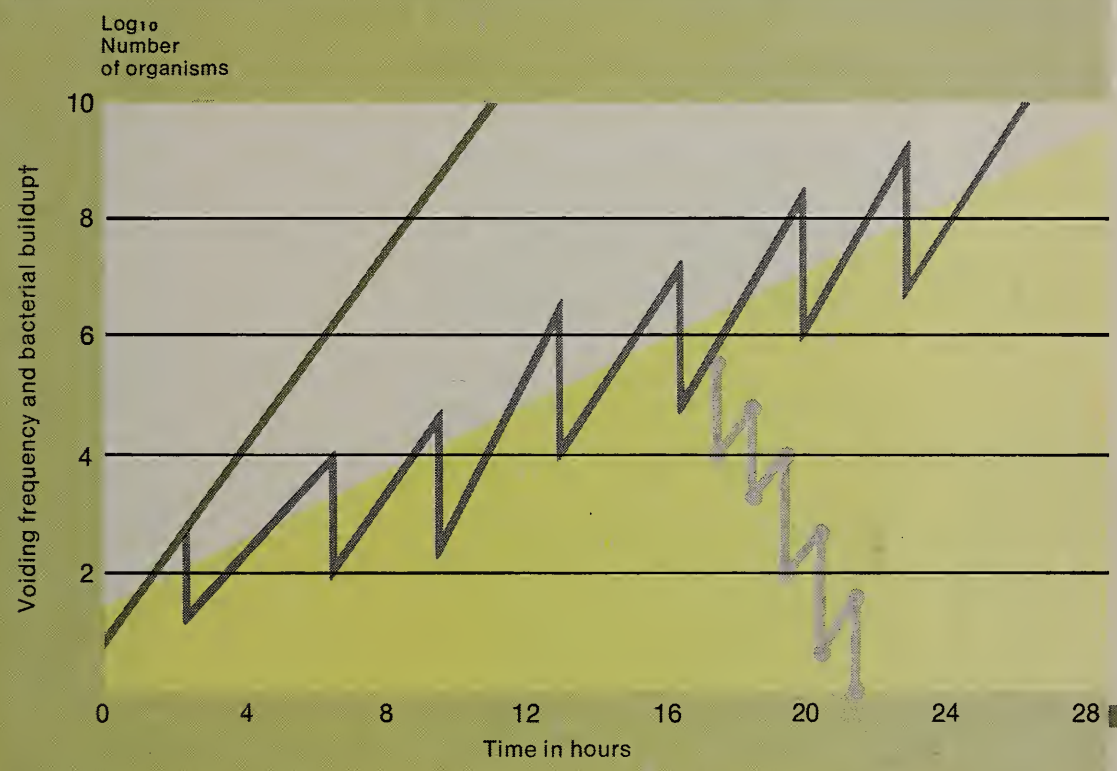


Chart shows the theoretical effect of various voiding frequencies on bacterial proliferation in the urine.

Maximum growth rate during the overnight period
Voiding every 3½ hours
Voiding every hour: the "washout" effect

†Adapted from O'Grady F, Cattell WR: *Brit J Urol 38*:156, 1966

For acute nonobstructed cystitis*

Gantanol® B.I.D.
sulfamethoxazole/Roche®

Basic therapy with convenience:

4 tablets (0.5 Gm each) STAT — then 2 tablets B.I.D. for 10-14 days

*due to susceptible organisms

(Continued from Page 37)

Mauna Kea Beach Hotel, Kamuela, Hawaii. Sunday-Wednesday. Contact: John S. Tytus, MD, 1118 9th Ave., Seattle 98101. (206) 223-6641.

October 3—**Glaucoma Surgery Workshop.** Jules Stein Eye Institute. Los Angeles. Friday. 6 hrs. $150. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

October 8—**Carcinoma of the Kidney, Adrenal, Retroperitoneum and Penis—3rd Annual Los Angeles Urological Cancer Conference.** See Cancer, October 8.

October 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 11-12—**Current Clinical Status of Hyperbaric Oxygen.** UCSF. Saturday-Sunday.

October 13-17—**American College of Surgeons—Clinical Congress.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: C. Rollins Hanlon, MD, 55 E. Erie St., Chicago, Ill. 60611.

October 18-19—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 21-December 2—**Surgical Anatomy and Surgery.** USC. Tuesdays.

October 24-25—**Retinal Symposium.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

October 24-25—**Orthopaedic Seminar: Management of Spine Pain.** Eisenhower Medical Center, Palm Desert. Friday-Saturday. 6 hrs. $50. Contact: Office of Medical Education & Research. Eisenhower Medical Center, 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

October 24-26—**Western Neurological Society.** Biltmore Hotel, Santa Barbara. Friday-Saturday. Contact: Calvin L. Rumbaugh, MD, or Hervey D. Segall, MD, L.A. County-USC Med. Center, 1200 N. State St., Los Angeles 90033. (213) 226-7425.

October 26-30—**Western Orthopedic Association.** Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. Contact: H. Jacqueline Martin, Exec. Sec., WOA, 1970 Broadway, Suite 1235, Oakland 94612. (415) 893-1257.

November 3-5—**Hereditary Disorders of the Eye—Annual Ophthalmology Course.** UCSF. Monday-Wednesday.

November 6-7—**Neurological Infections: New Clinical Approaches.** UCSF at VA Hospital, San Francisco. Thursday-Friday.

November 6-7—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

November 7-8—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

November 8—**Cleft Palate and Cranio-Facial Anomalies—7th Annual Symposium.** St. John's Hospital and Health Center, Santa Monica. Saturday. Contact: Kathy Harding, Asst. Coord,. Cleft Palate Service, St. John's Hospital and Health Center, 1328 22nd St., Santa Monica 90404. (213) 829-5511, ext. 2745.

November 8-9—**Muscle Relaxants.** American Society of Anesthesiologists at Marriott Hotel, Los Angeles. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

November 11-13—**Pediatric and Adolescent Aspects of Trauma.** See Pediatrics, November 11-13.

November 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 13-15—**Infections in Orthopedics.** STAN. Thursday-Saturday.

November 15—**Current Concepts in Ophthalmic Plastic Surgery: The Eye Lid.** UCLA. Saturday.

November 21-23—**Common Problems—Acute Hand Injuries.** UCLA. Friday-Sunday.

(Continued on Page 47)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin) is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, $T_3{}^{131}I$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Instructions for Use. The following conversion table lists the approximate equivalents of other thyroid preparations to Proloid (thyroglobulin) when changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), or T_4/T_3 (liotrix).

CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg)
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg)
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg)
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
Supplied. ¼ grain tablets in bottles of 100 (N0047-0250-51) and 1000 (N0047-0250-60); ½ grain tablets in bottles of 100 (N0047-0251-51) and 1000 (N0047-0251-60); scored 1 grain tablets in bottles of 100 (N0047-0252-51) and 1000 (N0047-0252-60); 1½ grain tablets in bottles of 100 (N0047-0253-51) and 1000 (N0047-0253-60); scored 2 grain tablets in bottles of 100 (N0047-0257-51); 3 grain tablets in bottles of 100 (N0047-0254-51) and 1000 (N0047-0254-60); scored 5 grain tablets in bottles of 100 (N0047-0255-51) and 1000 (N0047-0255-60). Full information is available on request. P-GP-51 4/c

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, N.J. 07950

Pro-Banthīne®
brand of
propantheline bromide

Indications: Pro-Banthīne is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution. Fever and possibly heat stroke may occur due to anhidrosis.

Overdosage may cause a curare-like action, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted. Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthīne.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may occur as well as mydriasis and blurred vision. In addition the following adverse reactions have been reported: nervousness, drowsiness, dizziness, insomnia, headache, loss of the sense of taste, nausea, vomiting, constipation, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult oral therapy is one 15-mg. tablet with meals and two at bedtime. Subsequent adjustment to the patient's requirements and tolerance must be made.

How Supplied: Pro-Banthīne is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680 481

(Continued from Page 42)

November 22—**Flexible Bronchofibroscopy.** PMC. Friday. 6 hrs. $300.

December 3-5—**Hereditary Disorders of the Eye—Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

December 5—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. $150. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

December 5-7—**Electronystagmography.** PMC at Regency Hyatt, San Francisco. Friday-Saturday.

December 5-9—**International College of Surgeons, U.S. Section—Annual Meeting.** Sheraton Waikiki, Honolulu. Friday-Tuesday. Contact: Mr. William A. Houser, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago. Ill. 60610. (312) 642-3555.

December 10-12—**Ocular Inflammatory Disease.** USC. Wednesday-Friday.

December 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

September 15-19—**New Ways to Foster Health and Human Well-Being.** Health Training Resources Center, California Dept. of Health, at 1625 Shattuck Ave., Berkeley. Monday-Friday. Contact: Health Training Resources Ctr., Calif. Dept. of Health, 2151 Berkeley Way, Berkeley 94704.

September 18-19—**Experimental Approaches to the Study on Manipulation Therapy.** UCI at Center for Health Education, Long Beach. Thursday-Friday.

September 19-20—**For the Physician in Private Practice: Strategies for Managing Hypertension.** See Medicine, September 19-20.

September 22-26—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

September 23-November 25—**Yoga: Clinical Applications and Techniques.** UCLA at 1620 Preuss Rd., W. Los Angeles. Tuesday, 7:30-10:00 p.m. 25 hrs. $85.

September 25—**Non-Traditional Sexually Transmitted Diseases.** VD Controllers, CMA VD Task Force at San Francisco Medical Society, San Francisco. Thursday. Contact: Erwin Braff, MD, S. F. Co. Health Dept., 101 Grove St., Room 307, San Francisco 94102. (415) 558-4877.

September 30-December 16—**Bedside Clinics.** USC. Tuesdays.

October 2-4—**Western Occupational Medical Association.** Sheraton Harbor Isle, San Diego. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 3-4—**Recent Trends in Management of Obesity.** UCSD. Friday-Saturday.

October 3-4—**Workshop on Aging.** American Geriatrics Society, UCSF at St. Francis Hotel, San Francisco. Friday-Saturday. 16 hrs. Contact: Workshop on Aging, 1429 Fourth Ave., San Francisco 94143. (415) 664-6929.

October 5-10—**American Physiological Society—26th Annual Fall Meeting.** Sheraton-Palace, San Francisco. Sunday-Friday. Contact: Mrs. Helena B. Lemp, APS, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-7010.

October 6-10—**Primary Care.** STAN. Monday-Friday.

October 7-8—**Paul M. Aggeler Lecture—6th Annual.** San Francisco General Hospital (7th) and UCSF (8th). Tuesday-

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE AND NATIONAL MIGRAINE FOUNDATION
DEPARTMENT OF NEUROLOGY
UNIVERSITY OF NEW MEXICO SCHOOL OF MEDICINE
SCRIPPS CLINIC AND RESEARCH FOUNDATION

CONTINUING EDUCATION IN PATHOGENESIS AND TREATMENT OF

Headache IN ADULTS AND CHILDREN

January 8, 9, 10, 1976— Albuquerque, New Mexico

COURSE DIRECTORS: *Otto Appenzeller,* M.D., Ph.D., Editor, HEADACHE: *Donald J. Dalessio,* M.D., President, Am. Assn. for the Study of Headache; *Ruth Atkinson,* M.D., Director, Pediatric Headache Clinic, UNM School of Medicine

FACULTY: *Seymour Diamond,* Chicago; *Arnold Friedman,* Tucson; *John Graham,* Boston; *Lee Kudrow,* Encino; *Robert S. Kunkel,* Cleveland; *Robert Ryan Jr.,* Rochester; *Robert Ryan Sr.,* St. Louis; *Dewey Ziegler,* Kansas City; *Donald Dalessio,* La Jolla; *Otto Appenzeller, Ruth Atkinson, Thomas Carlow, A. Earl Walker,* all Albuquerque.

—18 LECTURES: 3 case presentations; 2 evening panels; afternoons free.

—FEE: $195 ($95 for Interns, Residents and Fellows with letter from program director) must accompany registration. Cancellation charge $35 before Dec. 1. Mexican Fiesta Banquet included.

—15 HOURS AMA CONTINUING EDUCATION CREDIT CATEGORY I APPROVED.

Make cheques payable to "Headache Course": 1007 Stanford NE, Albuquerque, N.M. 87131; (505) 277-3342 for information, hotel reservations, program.

"CURRENT TOPICS IN DIABETES"

a postgraduate medical education course
co-sponsored by

THE DIABETES SOCIETY OF SANTA CLARA VALLEY
and
STANFORD UNIVERSITY SCHOOL OF MEDICINE
at

Rickey's Hyatt House, Palo Alto, California
DECEMBER 5 and 6, 1975

The symposium will present current knowledge of the basic mechanisms underlying various diabetic states and will deal in depth with management principles. The meeting is intended for primary physicians, including internists, family and general practitioners, emergency room physicians, endocrinologists, pediatricians, public health nurses, nurse educators, and nurse specialists in the field of diabetes. Eight hours of instruction will be provided.

Tuition for the course is $65 and advance registration is requested.

For further information and a brochure of the course please contact:

DIABETES SOCIETY OF SANTA CLARA VALLEY
2220 MOORPARK AVENUE
SAN JOSE, CALIFORNIA 95128
TELEPHONE (408) 287-3785

Wednesday. Visiting professor will be D. J. Weatherall, MD, Radcliffe Infirmary, Oxford, England. October 7—**Molecular Pathology of the Thalassaemia Disorders.** October 8—**Clinical and Genetic Aspects of the Control of Foetal Haemoglobin Production.** Contact: Susan Nutter, S.F. General Hospital, 1001 Potrero Ave., San Francisco 94110. (415) 648-8200, ext. 404.

October 8-11—**Medical Society of the United States and Mexico—23rd Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Saturday. Contact: Virginia E. Bryant, Exec. Sec., 333 W. Thomas Rd., Suite 207, Phoenix, Ariz. 85013.

October 9-11—**Wound Healing—Theory and Practice.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

October 9-30—**What to Tell Your Patients When They Ask About Acupuncture, Biofeedback and Hypnosis.** UCLA. Thursdays.

October 10—**American Geriatrics Society, Inc., Western Division—4th Annual Meeting.** Newporter Inn, Newport Beach. Friday. $35. Contact: Irving Hirshleifer, MD, 1080 N. Indian Ave., Palm Springs 92262. (714) 325-5044.

October 10-12—**Quality of Life—Today's Health Concern.** Calif. Society of Hospital Pharmacists, Hospital Assn., CMA, Calif. Nurses' Assn., Calif. Pharmaceutical Assn. at Hilton Hotel, San Francisco. Friday-Sunday. Contact: Paul Le Sage, U.S.P.H.S. Hospital, 15th Ave. & Lake, San Francisco 94118.

October 16-17—**Immunology for the Practicing Physician.** UCSF at Kaiser Center Auditorium, 300 Lakeside Dr., Oakland. Thursday-Friday.

October 17—**Antiplatelet Drugs and Thrombosis.** PMC at Miyako Hotel, San Francisco. Friday.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

October 18-19—**Review of Antimicrobial Therapy.** UCLA. Saturday-Sunday.

November 3, 4—**Death and Dying.** Eskaton American River Healthcare Center, Carmichael. Monday or Tuesday. $30. Contact: Roberta DeFrantz, RN, Dir., Staff Development, Eskaton American River Healthcare Center, 4747 Engle Rd., Carmichael. (916) 486-3211.

November 3-7—**Intensive Care.** STAN. Monday-Friday.

November 7-8—**Sports Medicine.** USC. Friday-Saturday.

November 9-12—**California Academy of Family Physicians.** Hotel Del Coronado, Coronado. Sunday-Wednesday. Contact: Mr. William W. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 13-14—**New Concepts in Medicine.** California Hospital Medical Center, Los Angeles. Thursday-Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Education, CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

November 15-16—**Crises Intervention—Part I.** UCLA. Saturday-Sunday.

November 20-22—**American Association for Automotive Medicine.** Sheraton Harbor Island, San Diego. Wednesday-Saturday. Contact: Albert Carriere, 801 Green Bay Rd., Lake Bluff, Ill. 60044.

November 30-December 4—**American Medical Association—29th Clinical Convention.** Sheraton Waikiki, Honolulu. Sunday-Thursday. Contact: AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

December 11-14—**Family Therapy for Family Physicians.** UCLA at Marina City Club, Marina Del Rey. Thursday-Sunday.

December 13-14—**Crises Intervention—Part II.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine,

Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

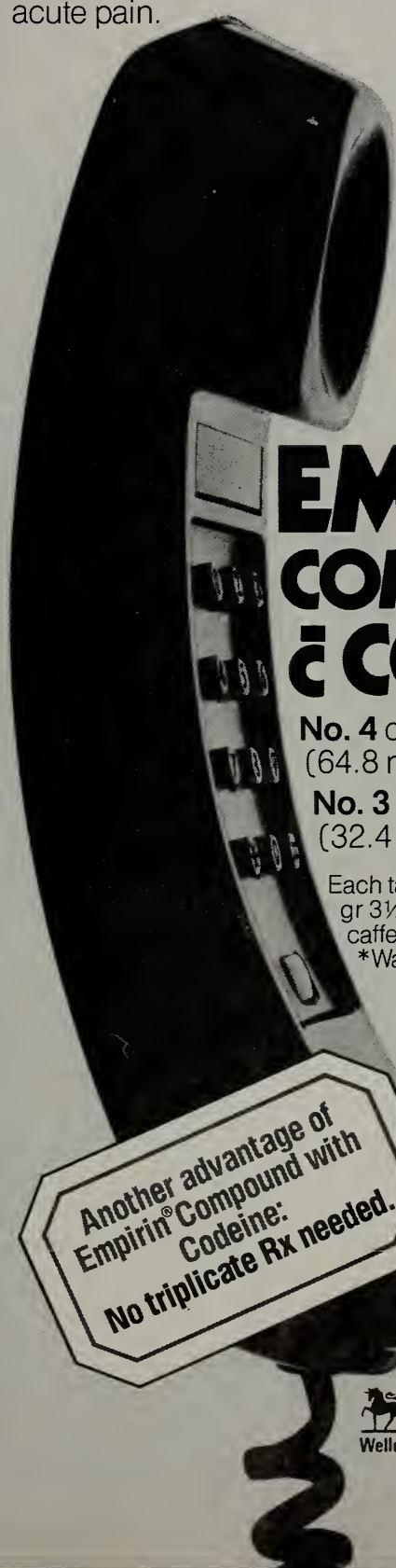
Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

Sept. 10-14—**Oregon Medical Association Scientific Session and House of Delegates.** Portland, Hilton Hotel. Contact:

The Pain Phone

When a telephone prescription for pain relief is necessary or convenient, you can call in your order for Empirin Compound with Codeine in 45 of the 50 states† That includes No. 4, which provides a full grain of codeine for more intense, acute pain.



†The exceptions: Alaska, Arizona, Maine, Oregon, Rhode Island, and the District of Columbia.

EMPIRIN® COMPOUND c̄ CODEINE

No. 4 codeine phosphate* (64.8 mg) gr 1

No. 3 codeine phosphate* (32.4 mg) gr ½

Each tablet also contains aspirin gr 3½, phenacetin gr 2½, caffeine gr ½.

*Warning—may be habit-forming.

CIII

Another advantage of Empirin® Compound with Codeine: No triplicate Rx needed.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

James A. Kronenberg, Oregon Medical Association, 2164 S. W. Park Place, Portland 97205, phone (503) 226-1555.

October 9—**Basic Mechanisms and Diagnosis of Pulmonary Disease.** Portland, Good Samaritan Hospital, Nursing Auditorium. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

October 15—**Adolescence and Its Problems.** Portland, Civic Auditorium. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

October 16—**The Psychology of Weight Loss.** Portland, Assembly Hall, Memorial Coliseum. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

November 7—**The Practical Management of the Patient with Coronary Disease.** Portland, Nursing Auditorium, Good Samaritan Hospital. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

September 15-16—**Liver and Cancer.** Monday-Tuesday. Univ. of Wash. Health Sciences Center, Seattle. 19 hrs. Fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 17-19—**Physical Therapy Clinical Education in Oncology.** Wednesday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours to be determined. $56.65. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 19-22—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan Knudson, Exec. Director, 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110.

September 26-27—**Arthritis Days '75.** Friday-Saturday. Olympic Hotel and Univ. of Wash. Health Sciences Center, Seattle. Limited to 150. 9 hrs. $40. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

September 26-27—**Review of Basic OB-GYN.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Div. of CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 1-June 9, 1975—**Internal Medicine Review.** Wednesday evenings, 6 p.m.-8 p.m., 35 weeks. Univ. of Wash. Health Sciences Center, Seattle. 70 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 2-3—**Team Effort in the Management of Cancer.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 2-4—**Montana State Medical Association Annual Meeting.** Thursday-Saturday. Fairmont Hot Springs Resort, Gregson, Montana. Contact: G. Brian Zins, Exec. Director, 2021 11th Ave., Suite 12, Helena, MT 59601.

October 4-5—**Workshop in Dermatological Surgery.** Saturday-Sunday. Univ. of Wash. Health Sciences Center, Seattle. Limited to 50. 14 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (296) 543-1050.

(Continued on Page 52)

DARVOCET-N® 100
propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

DARVON® COMPOUND-65
propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

500389

Relief from her arthritic pain

Darvocet-N® 100

0 mg. propoxyphene napsylate and
0 mg. acetaminophen

contains no aspirin

Darvon® Compound-65

5 mg. propoxyphene hydrochloride, 227 mg. aspirin,
62 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

for mild to moderate pain

ee summary of prescribing information on adjoining page.

(Continued from Page 21)

PRACTICE AVAILABLE

F.P., internal medicine, San Francisco peninsula, 30 years same location, $82,000 gross, $58,000 net, retiring Dec. 1975, will turn over practice free of charge, office fully equipped, hospital 1 mile, rent $500/month, 1,600 sq. ft., suitable for 2 physicians. Write Box 9428, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

39-YEAR-OLD, MARRIED, GENERAL MEDICAL PRACTITIONER, Board Eligible in Psychiatry seeks full time position in General Medicine and/or Psychiatry in Northern California coastal community. Extensive experience in Family Medicine, E.R. Medicine, Traumatology, and Community Psychiatry—especially Day Treatment and Substance Abuse. Excellent references. Box 9430, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES FOR LEASE OR RENT

SAN DIEGO—Suite ready for 1 or 2 physicians. Newly redecorated. Busy practice area. Call trading with nearby established physicians available. First 3 months' rent—only 10 percent of gross. R. C. Mowry, MD, 1300 Grand Ave., San Diego, CA 92109; (714) 273-4285.

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

MEDICAL SUITE FOR GROUP PRACTICE—Up to 4,000 sq. feet to be available in January, 1976. Located in South San Francisco. Reply Box No. 9431, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FOR

CLASSIFIED

INFORMATION

CALL

(415) 777-2000

(Continued from Page 50)

October 13-17—**Treating the Untreatable—Univ. of Washington School of Medicine's Eastern Washington Circuit Course.** Pullman, 13; Walla Walla, 14; Tri-Cities, 15; Yakima, 16; Wenatchee, 17. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

October 14-19—**American Society of Clinical Hypnosis Annual Meeting.** Tuesday-Sunday. Washington Plaza Hotel, Seattle. Contact: Ernest T. Guy, Exec. Director, 2400 East Devon Ave., Suite 218, Des Plaines, IL 60018. (312) 297-3317.

October 17-18—**Washington State Heart Association Symposium.** Friday-Saturday. Olympic Hotel, Seattle. Fee to be determined. Contact: De Loris Savage, R.N., Wash. State Heart Assoc., 333 1st Ave. W., Seattle 98119. (206) 285-2415.

October 30-31—**Office Management of Chronic Pain.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Limited to 50. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 6-7—**Learning Disabilities: Dilemma and Decisions.** Thursday-Friday—Univ. of Wash. Child Development and Mental Retardation Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir., CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 13-14—**Current Concepts in Drug Therapy.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours to be determined. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 4-5—**Life Saving Measures for the Critically Injured.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Limited to 200. 15 hrs. Practitioners, $150; interns, residents, $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

December 4-5—**Pacific Northwest Chapter, American College of Chest Physicians: Scientific Program.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 12-13—**Clinical Problems in Endocrinology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

Index to The Western Journal of Medicine Advertising

American Association for the Study of Headache and National Migraine Foundation
Headache Course 48
Ames Company
Diastix 3
Ayerst Laboratories
Premarin 44, 45
Boehringer Ingelheim Ltd.
Combipres 12, 13
Catapres 38, 39
Burroughs Wellcome Co.
Neosporin Topical 29
Empirin Compound with Codeine 49
Classified 20, 21, 52
Dairy Council of California 4
Geigy Pharmaceuticals
Butazolidin 35, 36
Eli Lilly and Company
Nebicin 14, 15, 16
Keflex 28
Darvocet-N 100 and Darvon Compound-65 .. 50, 51
Merck Sharp & Dohme
Aldomet 8, 9, 10
Triavil 22, 23, 24
Obetrol Pharmaceuticals
Obetrol 32
Pharmaceutical Manufacturers Association 6, 7
A. H. Robins Company
Allbee with C 17
Donnatal 18
Roche Laboratories
Valium ..... 2nd Cover and Page 1
Gantanol 40, 41
William H. Rorer, Inc.
Camalox 30, 31
Maalox ..... 4th Cover
G. D. Searle & Co.
Pro-Banthine 46, 47
Security Pacific Bank 11
Smith, Kline & French
Dyazide ..... 3rd Cover
Stanford University School of Medicine
The Diabetes Society of Santa Clara Valley 48
Warner Chilcott Laboratories
Proloid 42, 43
Westwood Pharmaceuticals Inc.
Pre-SUN 25
Wyeth Laboratories
Ovral 5
Bicillin/Wycillin 26, 27

THE WESTERN
Journal of Medicine

Refer to: Ayers LN, Ginsberg ML, Fein J, et al: Diffusing capacity, specific diffusing capacity and interpretation of diffusion defects. West J Med 123:255-264, Oct 1975

Diffusing Capacity, Specific Diffusing Capacity and Interpretation of Diffusion Defects

LARRY N. AYERS, MD, *Oklahoma City,*
MARVIN L. GINSBERG, MD, JERRY FEIN, MD, *and* KARLMAN WASSERMAN, MD, PhD,
Torrance, California

Six pathophysiologic mechanisms of a reduced single breath CO diffusing capacity are discussed and the usefulness of relating carbon monoxide (CO) uptake to the functioning alveolar volume (DL/VA, specific diffusing capacity) is illustrated for several pulmonary diseases. In patients with emphysema and pulmonary emboli (pulmonary vascular occlusive disease), reduced CO uptake is associated with significantly reduced DL/VA and is compatible with reduction of pulmonary capillary bed. In patients with pulmonary alveolar proteinosis, improvement in CO uptake and DL/VA follows lung lavage and suggests that lung units partially filled with proteinaceous material are responsible for hypoxemia, reduced CO uptake and reduced DL/VA. In most cases of radiation fibrosis, sarcoidosis and miscellaneous interstitial fibrosis, reduced CO uptake is associated with a normal DL/VA and suggests that loss of alveolar units, both capillaries and alveoli, has occurred. New regression equations for DL and DL/VA are established for children and adults. DL/VA is linearly related to height and independent of age and sex, while different predictive equations must be used for DL for the 5 through 17 and 18 through 76 age groups. The new regression equations for DL show better correlation in adults we studied over 50 years of age than previous regression equations which use a constant reduction of 2 to 3 ml CO per minute per mm of mercury for each 10 years of adult aging.

From the Respiratory Disease Division, Harbor General Hospital, Torrance, California and University of California, Los Angeles, School of Medicine.

Supported in part by USPHS Grant HL-11907. Also, supported in part by the California Research and Medical Fund—1972 (Dr. Ayers), by a fellowship of the Tuberculosis and Respiratory Disease Association of California (Dr. Ginsberg) and by a fellowship award of the Francis S. North Foundation (Dr. Fein).

Submitted, revised, May 1, 1975.

Reprint requests to: Larry N. Ayers, MD, Pulmonary Disease Section, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104.

ABBREVIATIONS USED IN TEXT

A-a = alveolar-arterial
DL = diffusing capacity of the lung for carbon monoxide
DL/VA = rate of carbon monoxide transfer per unit of alveolar volume (specific diffusing capacity)
VA = alveolar volume

THE PRIMARY FUNCTION of the lungs is to arterialize mixed venous blood. This is accomplished by exposure of blood in the lung capillaries to the alveolar air, a derivative of the gas exchange between the capillary blood and inspired air. In order to transfer oxygen molecules from atmospheric air to blood, the inspired air must enrich the oxygen in the alveolar gas to raise its partial pressure to levels above that in the blood entering the lungs. The transfer process entails diffusion of oxygen molecules across the alveolar-capillary membrane through the plasma into the red cell where it combines with hemoglobin. The rate of diffusion depends on (1) the difference between the partial pressure of the oxygen in the alveolus and the red cell, (2) the distance between the gas phase in the lungs and the red cell, (3) the gas exchange surface area and (4) the solubility of oxygen in lung tissue and plasma.

Therefore, the lungs' capacity to transfer oxygen from the inspired gas to the blood can be reduced due to (1) failure of the inspired gas to reach alveoli (poor distribution of ventilation), (2) loss of alveoli as a result of fibrosis and scarring of the entire gas exchange unit or lung resection, (3) enlarged alveolar spaces with reduction in gas exchange surface (emphysema), (4) a deficiency in red blood cells increasing the intravascular diffusion distance (anemia or abnormal hemoglobin), (5) loss of pulmonary capillary bed (thromboembolism or vasculitis) and (6) increase of the distance between the gas and blood phase of the functional lung unit due to filling of the alveoli by pathological material or thickening of the alveolar-capillary membrane resulting from interstitial fibrosis, inflammation or edema.

Today, carbon monoxide—a gas that has a much greater affinity for hemoglobin than oxygen, yet similar solubility characteristics—is the most frequently used test gas for measuring the diffusing capacity of the lungs.[1,2,5,9-12,15,16,18,20-22]

We have found that we could obtain more useful information from the single breath carbon monoxide (CO) diffusing capacity measurement by differentiating the six pathophysiological states described above and illustrated in Figure 1, all of which might cause a reduction in the transfer of CO as well as oxygen. It would be incorrect to equate all reductions in CO uptake rate to alveolar-capillary membrane thickening or a diffusion abnormality, an interpretation commonly made. Differentiation between the various factors which can cause a reduction in CO uptake rate is facilitated by the simultaneous measurement of the alveolar volume (VA) in which the CO is diluted and from which the CO might be absorbed.[11,19] Thus, the rate of CO transfer per unit of alveolar volume (specific CO diffusing capacity) might provide additional information regarding the pathophysiology of disease which results in a reduced diffusing capacity measurement. When one uses this measurement with those of alveolar gas uniformity[6] (single breath oxygen and nitrogen washout) measurements, physiological dead space, and hematocrit, considerable insight is gained with respect to the most likely pathophysiological state which might account for the reduction in CO uptake.

Because the values for the diffusing capacity of the lung for carbon monoxide (DL) for normal subjects at extreme ranges in age are scanty in the literature, we made measurements of DL and the rate of CO transfer per unit of alveolar volume (DL/VA) on 82 normal subjects between ages 5 and 76. Regression equations have been calculated. We find that for the extremes of ages, the normal values presented here are more representative than that in the literature. However, for subjects between 20 and 50 years old, there is little difference between our results and those in the literature. The purpose of this paper is to provide normal values for DL and DL/VA by the single breath technique in children and adults and to illustrate the use of the measurement of DL/VA to evaluate the physiological basis of a reduced DL.

Theoretical Considerations

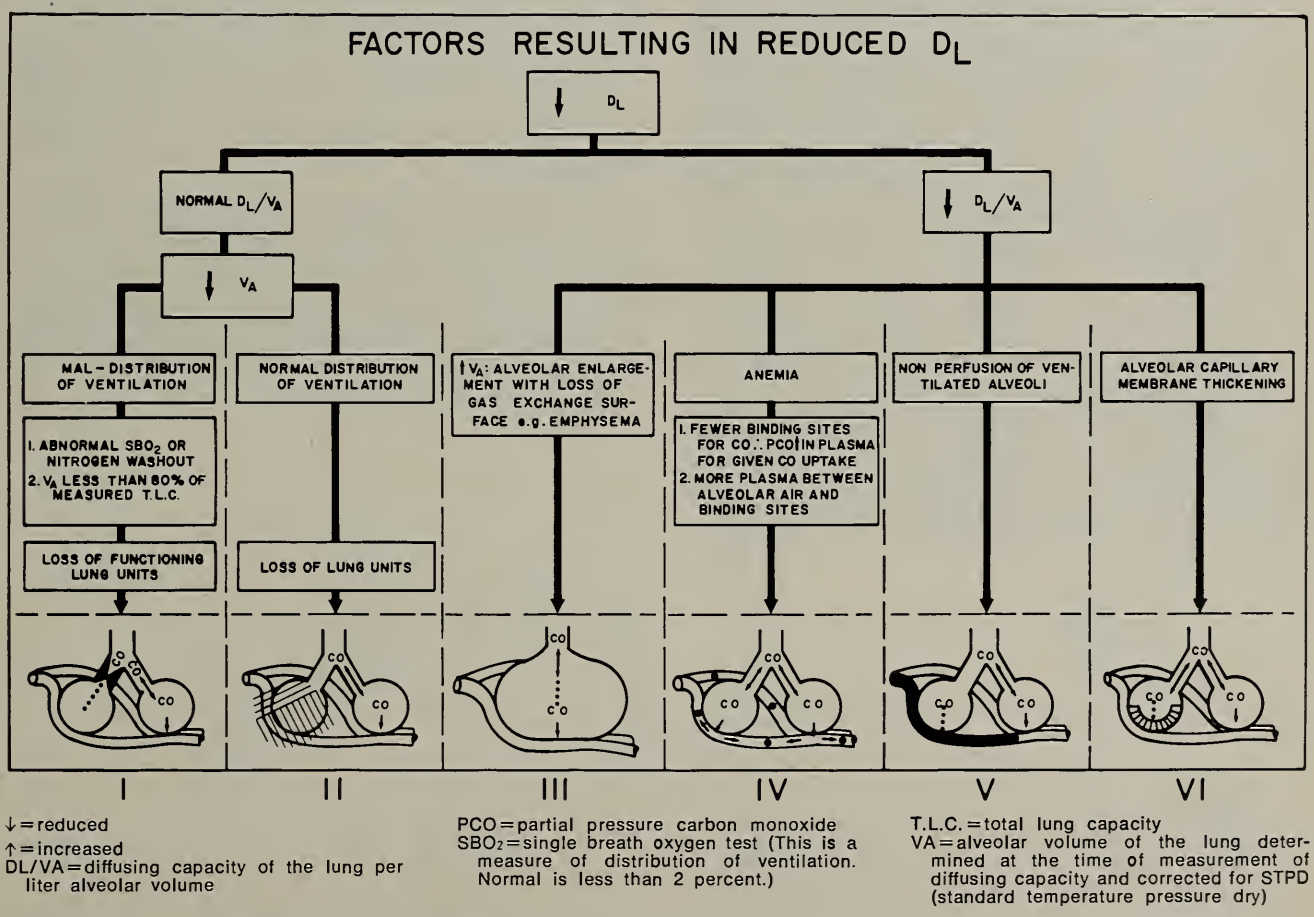
The pathophysiologic entities which can account for reductions in DL are described in Figure 1. A reduced DL can occur with a proportional reduction in alveolar volume (normal DL/VA) or with no reduction in alveolar volume (↓DL/VA).

A reduced DL, but normal DL/VA must be explained either by failure of the inspired gas to reach all of the normal diffusing membranes (Factor I, maldistribution of ventilation) or by

loss of lung units (Factor II, parenchymal fibrosis, or partial lung resection). In the case of Factor I, results of tests of distribution of ventilation would be abnormal, especially the single breath oxygen test (Comroe and Fowler). Also, in most cases, the alveolar volume would be less than 80 percent of the patient's actual total lung capacity. In the case of Factor II, the distribution of ventilation might be normal and the alveolar volume would usually be less than 80 percent of predicted total lung capacity.

Pathophysiological states in which DL and DL/VA are reduced fall into four categories. Commonly, patients with emphysema (Factor III) have enlarged alveolar spaces which receive part of the inspired gas during the single breath CO uptake test. Since the volume increases in the enlarged alveolar spaces as the cube of the radius while the surface area increases as the square of the radius (DL will be directly proportional to surface area), the ratio of DL to alveolar volume will decrease as the radius of the alveolus increases. A reduction of vascular supply to the emphysematous units without a comparable loss in ventilation will also result in a decrease in DL and DL/VA.

The rate-limiting factor in the uptake of CO by the blood is the number of red blood cells (hemoglobin) present in each milliliter of blood in the functioning pulmonary capillaries. The greater the number of red blood cells available per milliliter of blood, the less the time for CO molecules to encounter a red blood cell and be removed from its dissolved gaseous state. In anemia, (Factor IV) CO uptake is reduced because fewer red blood cells are present in each milliliter of blood and therefore diffusion distances in the liquid phase are increased. As a re-



↓=reduced
↑=increased
DL/VA=diffusing capacity of the lung per liter alveolar volume

PCO=partial pressure carbon monoxide
SBO_2=single breath oxygen test (This is a measure of distribution of ventilation. Normal is less than 2 percent.)

T.L.C.=total lung capacity
VA=alveolar volume of the lung determined at the time of measurement of diffusing capacity and corrected for STPD (standard temperature pressure dry)

Figure 1.—Schema illustrating the causes of a reduced diffusing capacity of the lung for carbon monoxide (DL). Factor I: failure of inspired gas to reach alveoli (maldistribution of ventilation); Factor II: loss of alveoli as a result of fibrosis and scarring of the entire gas exchange unit or lung resection; Factor III: enlarged alveolar spaces with reduction in gas exchange surface (emphysema); Factor IV: a deficiency in red blood cells increasing the intravascular diffusion distance (anemia or abnormal hemoglobin); Factor V: loss of pulmonary capillary bed (thromboembolism or vasculitis); Factor VI: increase of the distance between the gas and blood phase of the functional lung unit due to filling of the alveolar-capillary membrane resulting from interstitial fibrosis, inflammation or edema.

TABLE 1.—*Age and Sex Distribution of Subjects Used in This Study*

	Age		Number of Subjects: Male	Female
Normal				
Group 1	5-17	.....	12	9
Group 2	18-45	.....	22	10
Group 3	46-76	.....	15	14
Patients				
Group 1	20-50	Lymphoma treated with radiation ...	5	0
Group 2	23-74	Various pulmonary diseases	14	10

sult of the increased diffusion path due to anemia, the partial pressure of CO will increase in plasma and result in a decreased pressure gradient for CO transfer from the alveolar gas to the lung capillary. The presence of anemia can be easily determined and a correction can be made for this as described by Staub and co-workers.[23]

Vascular obstruction of aerated areas of the lungs (Factor V) decreases pulmonary capillary blood volume. Ventilation of these poorly perfused areas results in an increase in physiological dead space (wasted ventilation) and arterial-end tidal carbon dioxide (CO_2) differences. These abnormal physiological measurements can help separate this cause of a reduced DL from others.

Increased distance between capillary blood and alveolar gas space (Factor VI) could account for a reduction in DL/VA as well as DL during the standard single breath CO-diffusing capacity test. A classic example of reduced DL due to increased diffusion distance is alveolar proteinosis. In this condition, CO diffusion is reduced by a barrier of proteinaceous material which fills the alveolus and respiratory bronchioles. However, the physiological dead space and arterial-end tidal CO_2 differences are normal and reflect the normal vascular supply to the alveoli and the high solubility of CO_2 in the alveolar material.

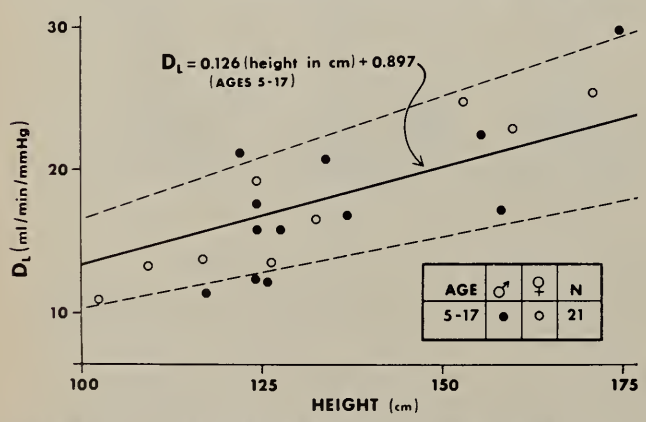


Figure 2A.—The relationship of diffusing capacity of the lung for carbon monoxide (DL) to height of normal children ages 5 through 17. Dashed lines are ± 25 percent of the points from the mean regression line. Correlation coefficient=.46; coefficient of variation=15 percent.

Methods

The CO diffusion capacity was measured by the single breath method.[11,19] The gas composition was 25.0 percent oxygen, 0.35 percent CO, 0.6 percent neon and the balance nitrogen. All samples of expired gas were analyzed with a gas chromatograph (Microtek, Tracor, or Hewlett-Packard).

To determine normal values for DL and DL/VA, 82 normal subjects were studied ranging in age from 5 to 76 years (Table 1). The subjects consisted of referrals undergoing pulmonary function studies as part of an annual or initial physical examination, hospital employees and family members of hospital employees. Selection criteria included no history of cardiopulmonary disease, no respiratory complaints, no anemia, normal vital capacity and forced vital capacity. Twenty percent of the subjects were smokers or ex-smokers of cigarettes.

Two groups of patients were studied, one consisting of five subjects with lymphoma before and after undergoing radiation therapy to the mediastinum and a second group of 24 patients with a variety of pulmonary pathological lesions (Table 1).

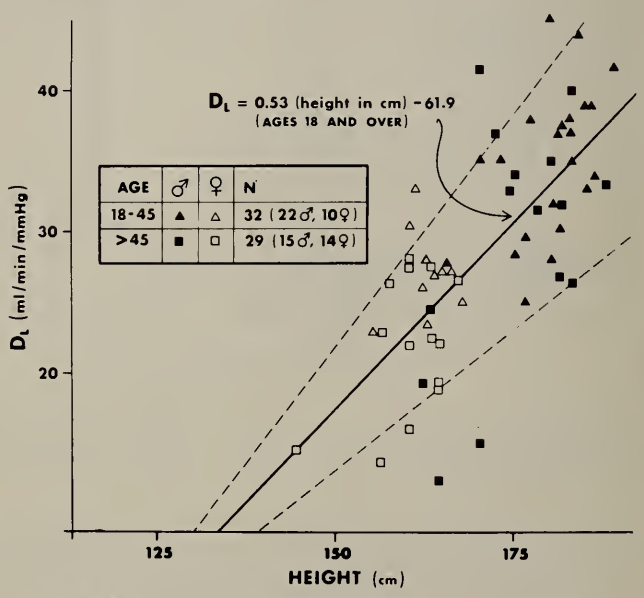


Figure 2B.—The relationship of DL to height of normal adults ages 18 through 76. Dashed lines are ± 25 percent of the points from the mean regression line. Correlation coefficient=.72; coefficient of variation=6 percent.

Results

Figures 2A and 2B show the relationship between DL and height in normal subjects ages 5 through 76. This relationship is not a linear one. Linear regression curves can be fitted to the data for children ages 5 through 17 (Figure 2A) and adults ages 18 through 76 (Figure 2B). In both sets of data, DL is independent of age and sex.

Figures 3A and 3B relate DL observed in our normal subjects over 50 years of age with the DL predicted from the literature[17] and from the regression equation of our normal adults over 18 years of age respectively. In Figure 3A, values in 17 of 26 persons are above 120 percent and in 1 of 26 below 75 percent of the literature's predicted DL. In Figure 3B, values in 4 of 26 are above 120 percent and in 4 of 26 are below 75 percent of the new predicted DL. Figure 3A shows that use of the constant reduction of 3 ml of CO per minute per mm of mercury for every 10 years increase in age will significantly underestimate DL in most patients over 50 years of age.

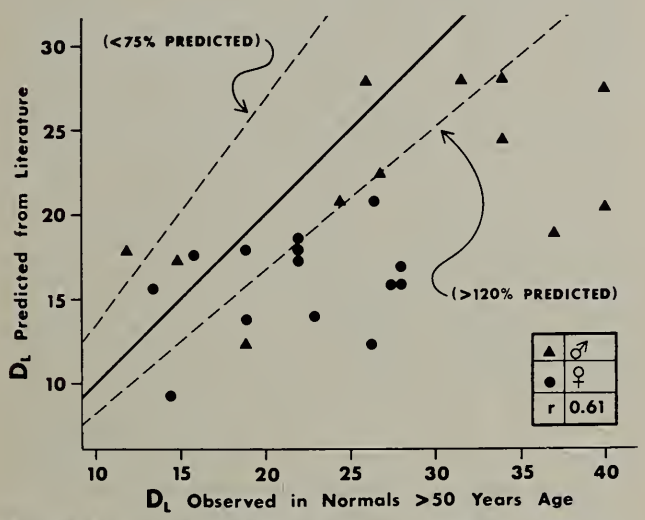


Figure 3A.—The relationship of observed diffusing capacity of the lung for carbon monoxide (DL) in normal adults over 50 years of age with DL predicted from data of McGrath and Thompson.[17] Dashed lines are less than 75 percent and more than 120 percent of the predicted DL.

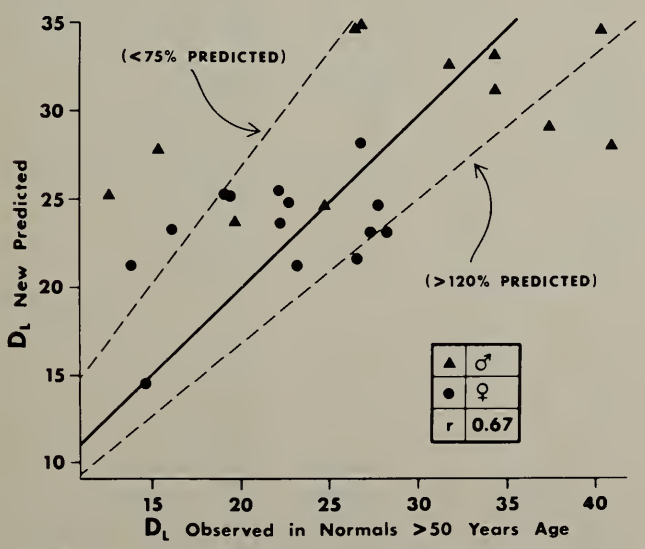


Figure 3B.—The relationship of observed DL in normal adults over 50 years of age with DL predicted from Figure 2B for adults (DL=0.53 [height in cm]—61.9). Dashed lines are less than 75 percent and more than 120 percent of the predicted DL.

Figure 4 shows the relationship between DL/VA (ratio of lung diffusing capacity to alveolar lung volume at the time of measurement as estimated by dilution of the inert gas in the test gas mixture) and height in normal subjects ages 5 through 76. This relationship is linear on an arithmetic plot and is unrelated to the age and sex of the subject. When expressed as DL/VA, the 5 to 17 year age group relates to height in the same way as adults. In contrast to DL, DL/VA decreases with height. This observation is compatible with the concept of the growth of alveoli rather than the increase in number of alveoli associated with the growth of the subject. Therefore, the ratio of surface area for absorption relative to the volume from which the gas is absorbed will decrease since the surface to volume ratio decreases with growth.

Patient Studies: Application and Interpretation

Interpretation of the DL/VA measurement is only indicated in the evaluation of a reduced DL. One can appreciate that hyperinflation (increased VA) with a normal pulmonary capillary bed (nor-

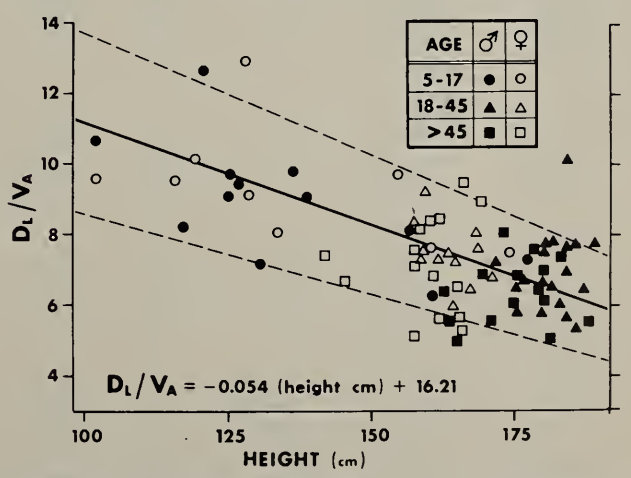


Figure 4.—The linear relationship of diffusing capacity of the lung per liter alveolar volume (DL/VA) to height. Dashed lines are ± 25 percent of the points from the mean regression line.

mal DL) will result in a reduced DL/VA. Also, poor subject cooperation during the DL measurement will result in underestimation of VA, normal DL and increased DL/VA.

Figure 5 shows the results of serial DL measurements on a group of five patients having radiation therapy for lymphoma. There is a sharp fall in DL within three months of irradiation. In contrast to the reduction in DL there is a lesser decrease in specific diffusing capacity (DL/VA), the reduction being within 75 percent of the control values in four subjects. This suggests that the reduction in DL is due mainly to a loss of lung units (alveoli and capillaries) rather than alveolar capillary membrane thickening (interstitial disease) as a major factor in the reduction of DL.

The effect of disease on DL and DL/VA is illustrated in Table 2. In *Cases 13, 17, 18, 20, 23 and 24* a reduction in DL is shown with an equal reduction in VA resulting in a normal specific diffusing capacity, while in *Cases 1 through 4 and 9 through 12* there is primarily reduction in DL without reduction in VA causing DL/VA to be reduced. The patients in whom DL/VA is reduced are primarily those patients with pulmonary vascular occlusive disease or emphysema.

Longitudinal studies in five patients representing four types of pathophysiology are illustrated in Table 3. The predicted values for DL/VA were obtained from Figure 4. In *Case 22* there was an increased alveolar-arterial (A-a) oxygen difference as well as low DL/VA in the early part of the patient's course. Since anemia (Factor IV) was not present, Factor V and Factor VI remain as the most likely causes of the reduced DL/VA in the patient (Figure 1). Subsequently, the patient's vital capacity and DL/VA improved slightly, while the alveolar-arterial oxygen difference improved to a much greater degree. We have commonly noted this as a disease goes from an acute or subacute to a chronic stage. A possible reason for the more striking improvements in the A-a oxygen difference than in DL is that the perfusion shifts as the inflamed lung units scar. Thus, DL would remain decreased since transfer of CO would be impaired whether the diseased lung unit was inflamed or scarred. However, the hypoxia would disappear as perfusion shifts in the conversion of inflammation to fibrosis.

Case 24 in Table 3 illustrates the course of a patient with Histiocytosis X lung disease. Various doses of steroids had been given throughout the course. DL/VA remained normal despite the abnormal alveolar-arterial oxygen differences and the low DL values. The severe abnormality in distribution of ventilation in this patient (Table 2) and the loss of lung units by scarring are most likely responsible for the reduction in DL. The

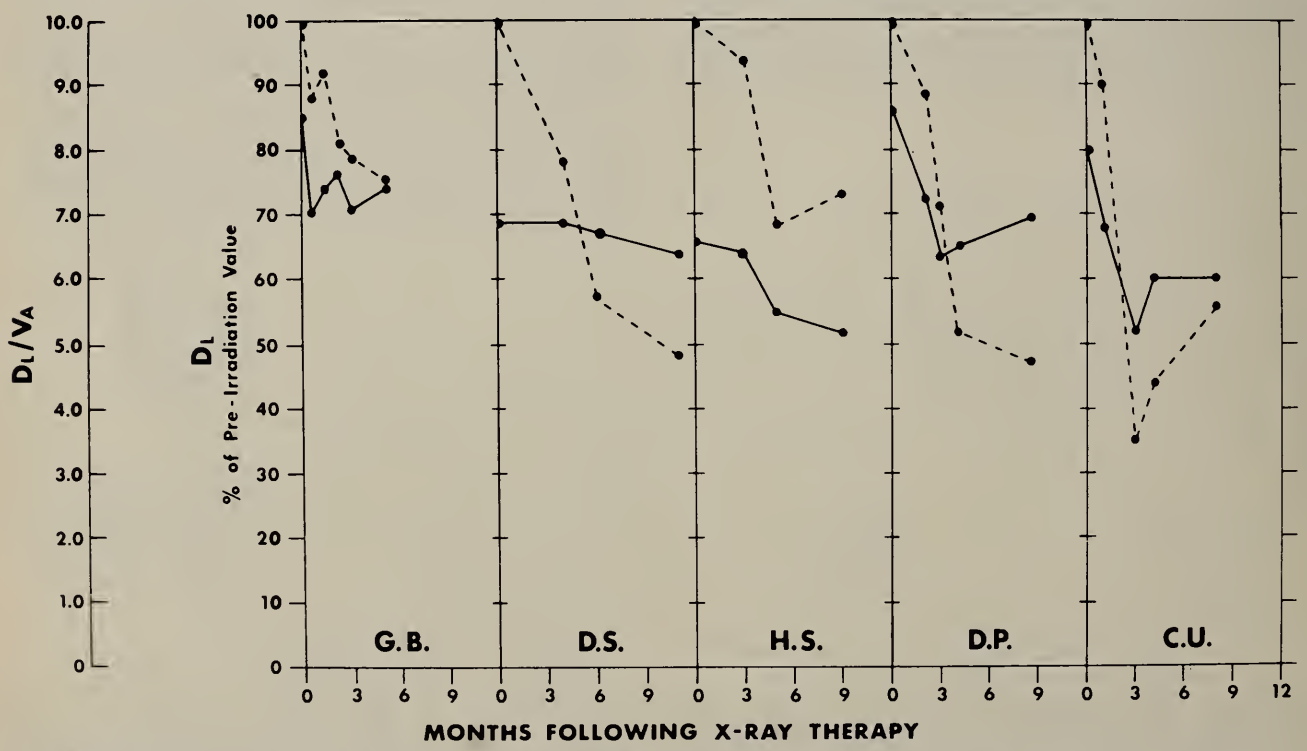


Figure 5.—Effect of radiotherapy on diffusing capacity (DL) and specific diffusing capacity (DL/VA) in five patients. DL is in solid lines and is represented as percent of pre-irradiation value while DL/VA is in dashed lines and is represented as diffusion per liter alveolar volume.

variable alveolar-arterial oxygen differences were correlated with periods of clinical improvement and exacerbation. Again, the persistently low DL values and near-normal DL/VA values are likely the result of scarring of lung units, (Factor I or Factor II) both vessels and alveoli.

Case 13 in Table 3 represents one type of pathophysiological defect which can occur in pulmonary alveolar proteinosis. In this patient, there was a pronounced reduction in vital capacity as well as a reduced DL. The DL/VA was within normal limits. The alveolar-arterial oxygen difference was moderately severely increased. This pathophysiological pattern suggests that those alveoli which are functioning, are able to absorb CO relatively normally. However, there had been a severe loss of functional lung units in the patient as evidenced by the reduced DL. Those that are not functioning are apparently filled with proteinaceous material which is equivalent to loss of lung units (Factor II). Perfusion apparently persists to a certain degree accounting for the increased alveolar-arterial oxygen differences. Findings on a biopsy study of the lungs confirm that the respiratory units from the alveolar membrane to the terminal bronchioles can be completely filled with the amorphous material characteristic of pulmonary alveolar proteinosis.

Case 14 (Table 3) is an example of the same disease but with somewhat different pathophysiology. There is apparently little loss in functional lung units since the vital capacity is normal. However, the DL/VA is reduced, suggesting that the proteinaceous material in the alveoli is inhibiting diffusion but not completely filling the functional lung unit (Factor V or VI). Treatment results in

TABLE 2.—*Effect of Disease on DL and DL/VA*

Case	*Sex, Height (cm), Age*	*Maximum Expiratory Flow Rate (Normal over 300 L/min)*	*Single Breath Oxygen (Normal less than 2%)*	*Seven Minute Nitrogen Washout (Normal less than 2%)*	*DL mlCO/ mmHg/min*	*Percent Predic.*	*DL/VA mlCO/ mmHg/min/L*	*Percent Predic.*	*Basis of Diagnosis**
EMPHYSEMA									
1	... ♂ 170.0 69	88	4.1	3.75	15.5	57	2.7	39.0	1,2,4
2	... ♂ 170.0 60	36	10.5	8.0	9.2	34	2.1	30.0	1,2,4,6
3	... ♂ 185.5 48	18	..	..	3.8	10	1.6	26.0	1,2,4
4	... ♀ 181.5 61	49	10.1	7.1	16.2	49	3.8	59.0	1,2,4
BRONCHIAL ASTHMA									
5	... ♂ 154.0 22	157	4.5	4.5	33.2	166	8.8	144.0	1,2,4
6	... ♀ 162.0 66	272	2.5	0.7	19.3	80	4.48	90.0	1,2,4
7	... ♂ 181.0 36	187	2.2	1.2	33.1	100	6.9	121.0	1,2,4
8	... ♀ 142.0 17	120	2.3	0.49	19.5	149	7.6	96.0	1,2,4
PULMONARY EMBOLI									
9	... ♀ 167.5 42	240	4.3	0.50	12.2	45	3.1	44.0	1,2,3,4,7
10	... ♂ 173.0 74	385	..	0.25	14.0	47	3.2	48.0	1,2,3,4,7
11	... ♂ 167.5 53	213	..	0.65	9.9	37	2.0	29.0	1,2,3,4,7,8
12	... ♂ 172.0 61	333	4.5	0.78	11.3	39	2.0	39.5	1,2,3,4,7
PULMONARY ALVEOLAR PROTEINOSIS									
13	... ♀ 160.0 23	320	1.0	0.5	7.4	31	6.2	83.0	1,5
14	... ♀ 165.0 42	..	6.0	0.85	8.2	31	3.1	43.0	1,5
15	... ♂ 179.0 34	384	2.0	0.5	19.4	61	6.6	67.0	1,5
16	... ♂ 184.0 26	428	3.3	0.4	10.3	29	7.1	48.0	1,5
SARCOIDOSIS									
17	... ♀ 160.0 38	300	1.0	0.7	16.7	70	6.88	89.0	1,4
18	... ♀ 165.0 60	160	5.5	0.5	9.2	35	4.8	90.5	1,3,4
19	... ♂ 176.0 38	91	6.5	0.4	22.4	72	8.8	144.0	1,3,4
20	... ♂ 180.0 25	300	4.0	0.4	17.3	52	5.8	100.0	1,3,4
MISCELLANEOUS INTERSTITIAL FIBROSIS									
21	... ♂ 173.0 63	320	9.0	0.4	10.9	36	4.8	70.0	1,2,3,4
22	... ♀ 158.5 18	240	..	0.55	6.7	29	4.3	57.0	1,4,5
23	... ♂ 188.0 46	375	1.36	0.79	12.2	33	5.59	108.0	1,2,3,4
24	... ♀ 183.0 31	31	7.7	7.3	11.4	33	5.2	84.0	1,5

*1=X-ray; 2=History and physical; 3=Clinical course; 4=Respiratory function testing; 5=Lung biopsy; 6=Postmortem; 7=Lung scan; 8=Cardiac catheterization.

DL=diffusing capacity of lung for carbon monoxide

DL/VA=diffusing capacity of lung for carbon monoxide per liter alveolar volume

improvement of both DL and DL/VA as well as arterial oxygenation.

The course and response to lung lavage in another patient with alveolar proteinosis is described in *Case 16* (Table 3). The pronounced reduction in diffusing capacity and in DL/VA is compatible with many lung units which are partially filled and functioning (Factor V or VI). Lung lavage results in removal of this proteinaceous material and consequently an increase in DL and DL/VA and reduction in the large alveolar-arterial oxygen difference.

Cases 1 through 4 (Table 2) illustrate characteristic findings in emphysema. Severe maldistribution of ventilation accompanies this disease. Reduction in DL/VA suggests that the reduced DL is due to a decreased capillary bed or enlargement of the alveolar spaces or both, and is not due solely to maldistribution of inspired carbon monoxide.

In asthma (*Cases 5 through 8,* Table 2), normal diffusing capacity and DL/VA are found. The observation of normal diffusion in obstructive airway diseases is compatible with a normal intact pulmonary capillary bed and contrast with the findings in emphysema.

Cases 9 through 12 (Table 2) are representative of multiple small pulmonary emboli and illustrate a very low specific diffusing capacity (DL/VA). Excluding ventilation abnormalities the factors that determine DL in the presence of pulmonary vascular obstruction are size of pulmonary vessels obstructed, presence or absence of bronchial collateral blood flow and location of emboli within the different zones of vascular perfusion in the lung.[25] Thus if the emboli are in larger vessels and the capillaries are open and contain red blood cells, DL will not be affected but if pulmonary capillaries are obstructed DL must decrease.

Cases 17 through 20 (Table 2) show that reduction in diffusing capacity with sarcoidosis is associated with loss of alveolar units and a relatively normal specific diffusing capacity. Could this reduction in DL merely reflect a reduction in alveolar volume without a loss of capillary bed? Against this argument are the observations by Miller and Johnson that in normal subjects DL is reduced from 0 to 12 percent when determined at half of total lung capacity.[26] The reduction of DL in *cases 17 through 20* is far greater than could be accounted for by low lung volumes alone and loss of alveolar units, both capillaries and alveoli, has occurred and resulted in the relatively normal specific diffusing capacity.

Cases of idiopathic interstitial fibrosis, (*cases 21 through 24,* Table 2) are most commonly associated with a reduced DL and alveolar volume. Therefore, DL/VA is commonly normal, but might be reduced to a lesser degree than DL.

TABLE 3.—*Abnormal Diffusing Capacity Measurements*

Date	Percent of Predict. V.C.	DL mlCO/mmHg/min.	DL Percent Predict.	DL/VA mlCO/mmHg/min/L	DL/VA Percent Predict.	Alveolar-Arterial O_2 Difference* mmHg
CASE 22 Diffuse Interstitial Fibrosis Height (cm) = 158.5						
9-26-67	29	6.7	29	4.3	57	50
10-10-67	34	5.6	24	3.6	48	45
11-7-67	40	7.6	33	4.8	63	26
11-27-67	49	9.0	39	5.7	75	24
12-19-67	55	9.4	41	5.8	77	27
1-11-68	60	8.8	38	4.5	60	..
2-1-68	59	8.6	37	4.4	58	25
CASE 24 Histiocytosis X Lung Disease Height (cm) = 183						
7-18-67	..	..	..	..	..	50
7-24-67	..	..	..	..	..	29
8-7-67	..	..	..	..	..	21
10-25-67	38	11.4	33	5.2	84	28
11-30-67	41	9.3	27	5.0	80	33
12-22-67	45	..	..	..	..	52
11-25-68	41	12.2	35	5.2	84	33
CASE 13 Pulmonary Alveolar Proteinosis Height (cm) = 160						
10-23-67	22	7.4	31	6.0	82	64
10-30-67	Left lung lavage					51
11-3-67	29	8.3	35	5.5	74	66
11-6-67	Right lung lavage					
11-9-67	44	12.0	50	6.8	92	21
11-21-67	..	9.4	39	5.5	74	..
2-6-68	62	13.6	57	6.8	92	24
CASE 14 Pulmonary Alveolar Proteinosis Height (cm) = 165						
6-2-66	96	8.2	32	3.1	43	70
6-13-66	Left lung lavage					
6-15-66	..	11.2	43	3.9	54	54
6-17-66	Right lung lavage					
6-20-66	104	14.0	54	4.1	58	35
9-8-66	116	19.6	82	5.1	71	10
CASE 16 Pulmonary Alveolar Proteinosis Height (cm) = 184						
5-1-73	63	10.3	29	3.4	48	54
5-3-73	Left lung lavage					
5-4-73	78	15.1	42	4.4	62	37
5-7-73	Right lung lavage					
5-8-73	80	20.2	56	5.5	78	24

*Normal alveolar-arterial O_2 difference <20 mmHg (Air-breathing at sea level).
VC = vital capacity
DL = diffusing capacity of the lung for carbon monoxide
DL/VA = diffusing capacity of lung for carbon monoxide per liter alveolar volume

Discussion

The diffusing capacity is a measure of the pathophysiology of the pulmonary disease process. One purpose of the paper is to point out the many factors which might cause the diffusing

capacity (DL) to be abnormal. A reduced DL may be present because of a loss of pulmonary capillaries to ventilated lung, anemia, alveolar-capillary membrane thickening or uneven distribution of ventilation.[2,13,14,17]

In this paper, we examine both DL and DL/VA as related to the simultaneously measured alveolar volume (specific diffusing capacity) in normal subjects and patients.

The relationship of diffusing capacity (DL) to lung volume in any given subject was first pointed out by Marie Krogh in 1915.[13] She noted that DL was constant below a lung volume which she called the mean capacity. Above this lung volume, DL increased. She thought that this was due to thinning of the alveolar-capillary membrane and consequently a shorter diffusion path as the alveoli enlarged.

In order to standardize the measurement of DL for clinical purposes, corrections in DL have been made with age, height, body surface area, sex and alveolar volume.[4,7,17] However, the scatter in these correlations is wide. In general, we find that the predictive values in the literature are underestimates for patients over the age of 55 years. Measurements in children are difficult to find.

McGrath and Thompson related their measurements to height and age in adults.[17] As expected, DL increases with height. However, we find that the use of a constant reduction of 3 ml of CO per minute per mm of mercury for each 10 years of adult aging as used by these investigators is not consistent with observations. It results in extremely low and unrealistic predicted values for elderly patients. Perhaps their older population was also a shorter population in height, thereby making a spurious negative correlation with age.

McGrath and Thompson[17] found that DL in women of a given height and age was 10 percent less than in men. However, Burrows and coworkers[4] found no relationship between DL and sex. The difference in the observation of these authors might be due to the lack of sufficient uniformity in the DL measurement in a given population. A 10 percent difference is probably just outside of the experimental error of measurement. We do not find statistical differences in DL in the two sexes when the values measured are related to height.

Teculescu and Stanescu found that DL in men was lower in smokers.[27] Although smoking appears to be a significant factor in a reduced DL only 20 percent of our adult subjects were smokers or exsmokers. Also the scatter of DL with height was less in our normal subjects (coefficient of variation = 6 percent) when compared with the regression equation of Teculescu and Stanescu[27] which plotted DL with height and age (coefficient of variation = 14.1 percent).

Our studies include measurements in normal children and normal adults taken from Harbor General Hospital and Stanford Medical Center and represent a wider age group than previously studied. In children ages 5 to 17 years and adults 18 to 76 years, DL is linearly related to height. Eighty-seven percent of the adults fall within ±25 percent of the predicted, whereas 76 percent of the children fall within ±25 percent of the predicted range. When Burrows and co-workers[4] established regression relationships with age and concluded that DL decreased with age, the scatter of their data was wide and the height factor was not standardized. There is a tendency for young adults to be taller than elderly adults.

Both in children and adults DL/VA is linearly related to height but unrelated to age (Figure 3). The average values for DL/VA in our studies closely agree with those of Burrows and associates.[4] However, their data show greater scatter than our own, probably because they standardized against age while we correlated our data to height.

Our data (Figure 4) demonstrate that the relationship of DL/VA and height correlated for pediatric as well as adult patients and is unrelated to the age and sex of the subject. The smaller the subject, the greater is the volume of CO extracted from each liter of alveolar volume. DL/VA of 5 was the lowest value obtained in our tallest subjects while 13.6 was the highest seen in our smallest subjects.

The significance of the relationship of DL to height might be that smaller subjects have smaller alveoli and therefore more surface area per liter of alveolar volume. Therefore, more CO could be absorbed since the absorbing surface per liter of alveolar volume would be greater than that for taller subjects. Since the total number of alveoli remains constant after age seven,[8,24] the subsequent enlarging alveolar volume during growth increases as the cube of the radius while the surface area only increases as the square of the radius. Thus, alveolar volume would increase with growth out of proportion to absorbing surface.

We feel that the specific diffusing capacity or

the CO extracted per liter of alveolar volume (DL/VA) is useful for gaining a better understanding of the pathophysiology associated with a reduced DL.

REFERENCES

1. Bates DV: The uptake of carbon monoxide in health and emphysema. Clin Sci 11:21-32, 1952
2. Bates DV, Varvis CJ, Donevan RE, et al: Variations in the pulmonary capillary blood volume and membrane diffusion component in health and disease. J Clin Invest 39:1401-1412, 1960
3. Bucci G, Cook CD, Barrie H: Studies of respiratory physiology in children. J of Peds 58:820-828, 1961
4. Burrows B, Kasik JE, Niden AH, et al: Clinical usefulness of the single breath pulmonary diffusing capacity test. Am Rev Resp Dis 84:789-806, 1961
5. Cohn JE, Carroll DG, Armstrong BW, et al: Maximal diffusing capacity of the lung in normal male subjects of different ages. J Appl Physiol 6:588-597, 1954
6. Comroe JH Jr, Fowler WS: Detection of uneven ventilation during a single breath of O_2. Am J Med 10:408-413, 1951
7. Donevan RE, Palmer WJ, Varvis CJ, et al: Influence of age on pulmonary diffusing capacity. J Appl Physiol 14:483-492, 1959
8. Dunhill MS: Postnatal growth of the lung. Thorax 17:329-333, 1962
9. Filley GF, MacIntosh DJ, Wright GW: CO uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. J Clin Invest 33:530-539, 1954
10. Forster RE: Exchange of gases between alveolar air and pulmonary capillary blood: Pulmonary diffusing capacity. Physiol Rev 37:391-452, 1957
11. Forster RE, Cohn JE, Briscoe WA, et al: A modification of the Krogh Carbon Monoxide Breath Holding Technique for estimating the diffusing capacity of the lungs: A comparison with three other methods. J Clin Invest 34:1417-1426, 1955
12. Forster RE, Fowler WE, Bates DV, et al: The absorption of carbon monoxide by the lungs during breath holding. J Clin Invest 33:1135-1145, 1954
13. Krogh M: The diffusion of gases through the lungs of man. J Physiol 49:271-300, 1914
14. Kruhoffer P: Lung diffusion coefficient for CO in normal human subjects by means of $C^{14}O$. Acta Physiol Scandinav 32: 106-123, 1954
15. Lewis B, Lin TH, Noe FE, et al: The measurement of pulmonary capillary blood volume and pulmonary membrane diffusing capacity in normal subjects: The effect of exercise and position. J Clin Invest 37:1061-1070, 1958
16. Marks A, Cugell DW, Cadigan JB, et al: Clinical determination of the diffusion capacity of the lungs: Comparison of methods in normal subjects and patients with alveolar-capillary block syndrome. Am J Med 22:51-73, 1957
17. McGrath M, Thompson ML: The effect of age, body size and lung volume change on alveolar-capillary permeability and diffusing capacity in man. J Physiol 146:572-582, 1959
18. McNeill RS, Rankin J, Forster RE: The diffusing capacity of the pulmonary membrane and the pulmonary capillary blood volume in cardiopulmonary disease. Clin Sci 17:465-482, 1958
19. Ogilvie CM, Forster RE, Blakemore WS, et al: A standardized breath holding technique for the clinical measurements of the diffusing capacity of the lung for carbon monoxide. J Clin Invest 36:1-17, 1957
20. Riley RL, Shepard RH, Cohen JE, et al: Maximal diffusing capacity of the lungs. J Appl Physiol 6:573-587, 1954
21. Ross JC, Frayser R, Hickam JB: A study of the mechanism by which exercise increases the pulmonary diffusing capacity for carbon monoxide. J Clin Invest 38:916-932, 1959
22. Roughton FJ, Forster RE: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to the true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 11:290, 1957
23. Staub NC, Bishop JM, Forster RE: Importance of diffusion and chemical reaction rates in O_2 uptake in the lung. J Appl Physiol 17:21-27, 1962
24. Weibel ER: Morphometry of the Human Lung. Academic Press, Inc, 1963, p 63
25. Nadel JA, Gold WM, Burgess JH: Early diagnosis of chronic pulmonary vascular obstruction. Am J Med 44:16-25, 1968
26. Miller JM, Johnson RL Jr: Effect of lung inflation on pulmonary diffusing capacity at rest and exercise. J Clin Invest 45:493-500, 1966
27. Teculescu DB, Stanescu DC: Lung diffusing capacity: Normal values in smokers and non-smokers using the breath-holding technique. Scan J Resp Dis 51:137-149, 1970

Maternal and Child Health Programs

The Division of Maternal and Child Health of the University of California School of Public Health at Berkeley has announced the following postgraduate programs for pediatricians, obstetricians and other physicians interested in receiving training in the field of maternal and child health. These programs all lead to the degree of Master of Public Health. Tax-exempt fellowship support is available.

Maternal and Child Health. A nine-month program in planning, organizing and operating comprehensive health services for mothers and children.

Family Planning. A nine-month academic program providing intensive work in family planning as part of the general graduate preparation of maternal and child health specialists.

School Health. A nine-month academic program providing intensive work in school health as part of the general graduate preparation of maternal and child health specialists.

The Multiply Handicapped and Mentally Retarded Child. A 21-month academic and clinical program in planning, organizing, and operating community services for children with multiple handicaps, including mental retardation.

Career Development Programs. Three-year academic and residency programs consisting of one year of academic training leading to the degree of Master of Public Health combined with residency training in Pediatrics or Obstetrics-Gynecology.

Applications are now being accepted for the group entering in July or September 1976. For information, write to Helen M. Wallace, MD, School of Public Health, University of California, Berkeley, CA 94720.

Refer to: Shaub M, Wilson R: The ultrasonic evaluation of nonfunctioning thyroid nodules. West J Med 123:265-268, Oct 1975

The Ultrasonic Evaluation of Nonfunctioning Thyroid Nodules

MICHAEL SHAUB, MD, *and* ROBERT WILSON, MD, *Los Angeles*

Thyroid echography was carried out on 100 patients with thyroid abnormalities to evaluate the diagnostic accuracy of ultrasound in differentiating simple thyroid cysts from solid thyroid nodules.

In all 46 proven cases, the ultrasonic diagnosis of the solid or cystic nature of thyroid nodules was correct.

A proposed diagnostic workup of a hypofunctioning (cold) thyroid nodule is suggested with primary needle aspiration and cytologic examination of the cyst fluid being recommended if the nodule is shown to be entirely cystic by ultrasound.

SOLITARY HYPOFUNCTIONING THYROID NODULES have long posed a diagnostic dilemma for clinicians and surgeons. Several workers[1-6] have shown the efficacy of the noninvasive modality of ultrasound in the differentiation of the solid from the cystic nature of a solitary hypofunctioning thyroid nodule that is greater than 1.5 cm in diameter. This report summarizes our experience with solitary thyroid nodules and the role of ultrasound in patient management and treatment.

Methods and Materials

Thyroid echography was carried out at the Los Angeles County, University of Southern California Medical Center in 100 patients with thyroid abnormalities. Most of the patients were referred for ultrasonic evaluation of a solitary hypofunctioning thyroid nodule (cold nodule). Approximately 15 percent of the patients studied were referred from the internal medicine service for evaluation of solitary, clinically palpable thyroid nodules. The study was undertaken to determine the reliability of diagnostic ultrasound in distinguishing a simple cyst from all other nodules.

No patient preparation was necessary. The patients were studied with a commercially available ultrasonic scanner. All the patients were studied by means of two-dimensional or B-mode echography. A compound contact scanner with a nonfocussed 2.25 megahertz transducer was used in all patients. Each patient was studied in the recumbent position with the neck hyperextended by a pillow placed beneath the patient's shoulders and neck (Figure 1). Mineral oil was used as the coupling agent in all cases. The scans were done transversely across the neck at low, intermediate and high gain settings. The criteria used to diagnose cystic and solid lesions were the standard ones. Cysts were diagnosed on the basis of (1) persistent sonolucency with high gain settings, (2) a well-defined, smooth posterior wall and (3)

From the Department of Radiology, Section of Diagnostic Ultrasound, Los Angeles County/University of Southern California Medical Center, Los Angeles.

This paper was presented, in part, at the scientific session of the 19th annual meeting of the American Institute of Ultrasound in Medicine, Seattle, Washington, October 1974.

Submitted March 11, 1975.

Reprint requests to: Michael S. Shaub, MD, Los Angeles County/USC Medical Center, P.O. Box 717, 1200 North State Street, Los Angeles, CA 90033.

Figure 1.—A patient is shown being examined in the recumbent position with neck extended by a pillow beneath the shoulders and neck. An obvious thyroid nodule is easily seen.

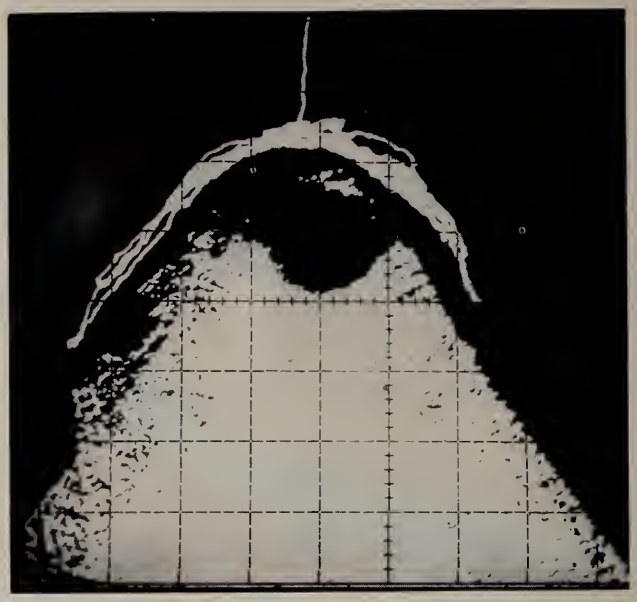


Figure 2.—(Case 1) A transverse scan of a typical cystic lesion is seen with a well-defined posterior wall, no echoes within the nodule and enhanced transmission through the lesion. The vertical line indicates the midline of the patient's neck. The grid lines are 1.5 cm per division. This nodule was surgically proven to be a colloid cyst.

enhanced transmission through the lesion (Figures 2, 3, 4). Solid lesions were diagnosed if (1) scattered or random internal echoes appeared within the lesion at intermediate to high gain settings, (2) a poorly defined posterior wall was present and (3) there was a lack of enhanced transmission through the lesion (Figures 5, 6). Multicystic lesions and solid lesions containing a cystic area were rejected in that percutaneous aspirations were to be carried out only on the simple cystic lesions. Adherence to these criteria is absolutely essential to the differentiation of solid versus cystic nodules. One exception was the simple cyst with an obvious internal septum.

The patients were instructed not to swallow or breathe deeply while the scan was being done. The position of head and neck was immobilized voluntarily. Great care was exercised to avoid distortion of the anatomy or movement of the thyroid nodule by applying excessive pressure to the skin with the transducer, or loss of acoustic contact with the skin. Both of these technical errors can cause artifactual echoes within a cystic lesion with resultant unnecessary thyroid cyst surgical operation. The procedure described is simple, safe and quick. The total length of the scanning procedure did not exceed five minutes in any patient and usually was two to three minutes.

Results

In 30 of the patients with solitary hypofunctioning nodules, there was pathologic proof. This consisted of either percutaneous needle aspiration of the cyst fluid or surgical pathologic proof. The fluid obtained by aspiration was routinely sent for cytologic examination. These 30 cases consisted of 7 cystic nodules (23 percent) and 23 solid thyroid nodules (77 percent). The group of 23 solid nodules was composed of colloid nodules (4 cases), adenomata (11 cases) and carcinoma (8 cases). In addition, three other preoperatively diagnosed cystic lesions were surgically proven to be thyroglossal duct cysts (Table 1).

There were 13 cases with clinically palpable thyroid nodules studied that, during subsequent studies, were determined to represent multinodular goiter with a single prominent nodule (12 cases) and Plummer's disease (1 case). These patients were referred to diagnostic ultrasound before radionuclide examinations were done. The remaining 54 patients are either on suppressive therapy, being evaluated for surgical procedures, or lost to follow-up.

It should also be mentioned that the clinical determination, by palpation, of the cystic or solid nature of a lesion is not reliable. There were numerous instances where the clinical impression was that of a cystic thyroid nodule and the lesion

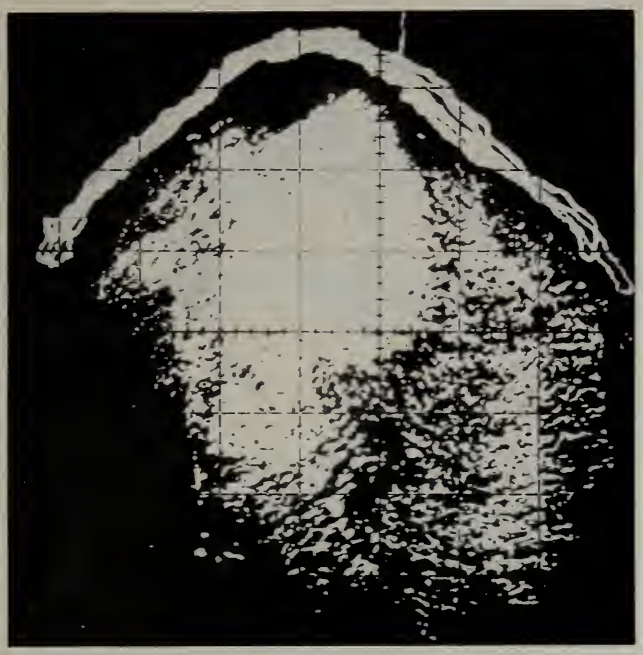


Figure 3.—(Case 2) A transverse scan showing a very superficial cystic lesion. The grid lines are 2 cm per division. This nodule was surgically proven to be a thyroglossal duct cyst.

was shown by ultrasound to be solid. There were also several instances where the clinical impression was that the nodule was solid and with echography it was shown to be cystic.

There were nine percutaneous aspirations on seven of the cystic thyroid lesions with one patient having three aspirations because of recurrence of the cyst. In two of the patients, surgical operations were carried out subsequently and the pathologic diagnoses in both of these cases were colloid cysts. As previously mentioned, three other ultrasonically diagnosed cysts proved to be thyroglossal duct cysts at subsequent surgical operation. All 10 proven cystic lesions, and all 23 proven solid lesions were correctly diagnosed. The prominent nodule in the multinodular glands and the nodule of Plummer's disease were also correctly diagnosed as being solid.

TABLE 1.—*Pathological Diagnoses in 33 Patients*

Pathological Diagnosis	*No. of Cases*	*Ultrasonic Diagnosis*		*Surgical Findings or Aspiration*	
		Solid	*Cystic*	*Solid*	*Cystic*
Colloid nodules	4	4	..	4	..
Adenomata	11	11	..	11	..
Carcinoma	8	8	..	8	..
Aspirated Cystic Nodules (with negative cytology)	7	..	7	..	7
Thyroglossal Duct Cysts	3	..	3	..	3
TOTAL	33	23	10	23	10

Figure 4.—(Case 3) A transverse scan over the patient's thyroid nodule. The lesion has the required cystic characteristics. The linear echo in the midportion of the nodule is typical for a septation. The grid lines are 2 cm per division. This nodule was proven to be cystic by aspiration.

Discussion

The introduction of isotopic scanning was a significant advance in the evaluation of a palpable thyroid nodule. This allowed differentiation of hyperfunctioning (hot) nodules from hypofunctioning (cold) nodules. This distinction is important because approximately 25 percent of all solitary nodules are hyperfunctioning[5] and the risk of malignancy in a hyperfunctioning nodule is extremely remote.

Solitary hypofunctioning (cold) thyroid nodules are composed of a heterogeneous group of lesions which includes both benign and malignant solid tumors, and benign thyroidal cysts. The reported frequency of malignancy in patients with hypofunctioning thyroid nodules varies depending upon their age; however, approximately 20 percent of patients with a nonfunctioning or cold thyroid nodule will have a malignant lesion,[7] and the incidence of solitary intrathyroidal cysts is approximately 20 percent of solitary hypofunctioning nodules.[5,8] The differentiation of the cystic or solid nature of a hypofunctioning thyroid nodule is of importance because of the far less risk of malignancy (approximately 1 to 2 percent) in solitary intrathyroidal cysts than in solid lesions.[5,8] The traditional management of a hypofunctioning

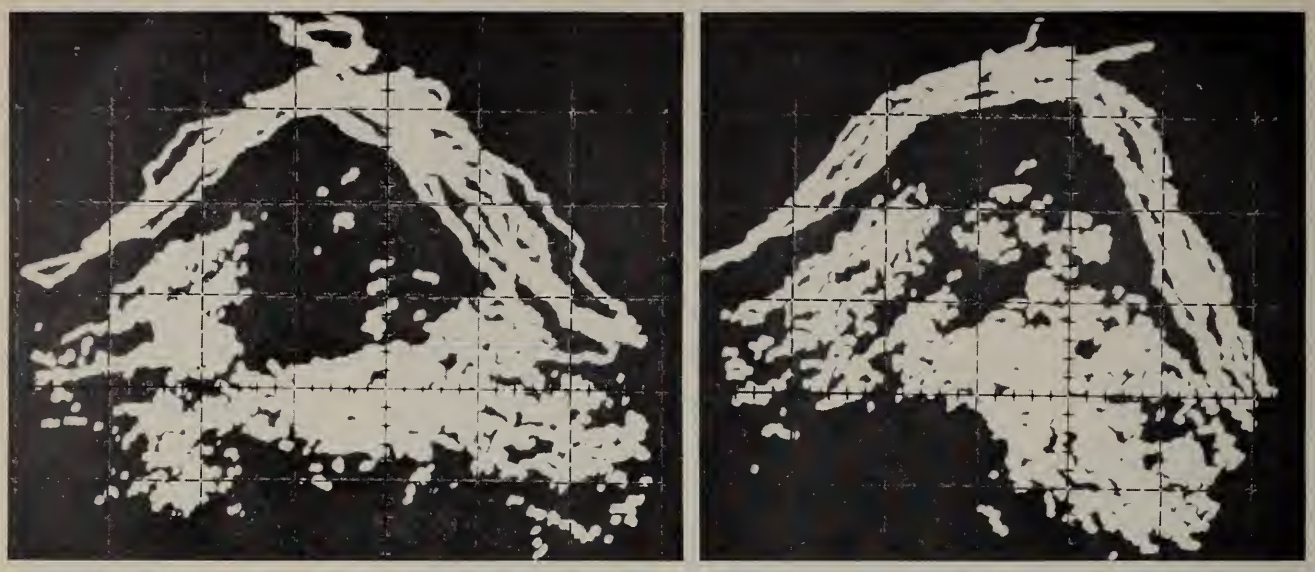


Figure 5.—(Case 4) **Left,** transverse scan, at a lower gain setting, showing characteristics of a solid nodule with internal echoes seen within the nodule. **Right,** transverse scan at a higher gain setting. More internal echoes can be identified, there is an irregular posterior wall and there is a lack of enhanced transmission through the lesion (compare with Case 1, Figure 2). The grid lines are 1.5 cm per division. This nodule was surgically proven to be a thyroid carcinoma.

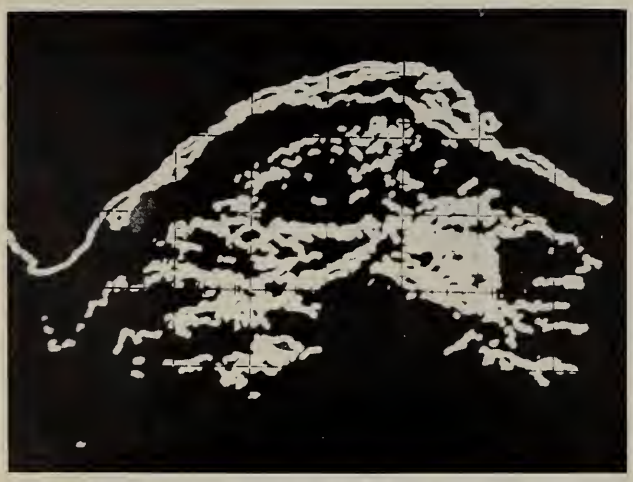


Figure 6. (Case 5). A transverse scan of a right-sided thyroid nodule. Even at this relatively low gain setting, internal echoes can be seen within the nodule. The grid lines are 1.5 cm per division. This nodule was surgically proven to be a thyroid adenoma. It should be noted that this nodule is ultrasonically the same as the previously shown thyroid carcinoma (Case 4, Figure 5). The differentiation by ultrasound between thyroid adenomas and thyroid neoplasms is not yet possible.

thyroid nodule noted on a radioisotope scan has been to consider the lesion malignant until proven otherwise (by surgical pathologic proof of the benign or malignant nature of the lesion). Now, with the advent of ultrasound as a noninvasive diagnostic tool, the cystic or solid nature of a hypofunctioning thyroid nodule can easily be determined.

Our experience, as well as the results of other investigators,[1-5] confirm the accuracy of ultrasound in identifying cystic thyroid nodules. Consequently, we feel that the most rational approach to the workup of a solitary palpable thyroid nodule greater than 1.5 cm in diameter would begin with a radioisotope scan. If the lesion is shown to be hypofunctioning, the patient should next be given an ultrasound examination. If the lesion is then shown to be cystic, the treatment should be conservative with primary needle aspiration and cytologic examination of the cyst fluid. This diagnostic workup will avoid the unnecessary expense and risk of thyroid surgical operation in a patient with a benign intrathyroidal cyst. Should the ultrasound examination show that the nodule is solid, then the usual course of workup and therapy may be pursued. In all cases, however, the addition of diagnostic ultrasound to the workup will allow a significant number of patients to be spared the risks of general surgical procedures.

REFERENCES

1. Blum M, Goldman AB, Herskovic A, et al: Clinical applications of thyroid echography. N Engl J Med 287:1164-1169, 1972
2. Thijs LG: Diagnostic ultrasound in clinical thyroid investigation. J Clin Endocrinol Metab 32:709-716, 1971
3. Rasmussen SN, Cristiansen NJB, Jorgensen JS, et al: Differentiation between cystic and solid thyroid nodules by ultrasonic examination. Acta Chir Scan 137:331-333, 1971
4. Blum M, Hernberg J: Pertinence of combined ultrasonic and isotopic scanning of the thyroid gland. J Nuc Med 12:418, 1971
5. Miskin M, Rosen I, Walfish P: B-Mode ultrasonography in assessment of thyroid gland lesions. Ann Intern Med 79:505-510, 1973
6. Editorial: Newer methods for evaluating thyroid nodules. N Engl J Med 287:1197-1198, 1972
7. Werner SC, Ingbar SH (Eds): The Thyroid: A Fundamental and Clinical Text, 3rd Ed. New York, Paul B. Hoeber, Inc, 1971, p 450
8. Crile G: Treatment of thyroid cysts by aspiration. Surgery 59:210-212, 1966

Refer to: Foran RF, Shore EH, Levin PM, et al: Bovine heterografts for hemodialysis. West J Med 123:269-274, Oct 1975

Bovine Heterografts for Hemodialysis

ROBERT F. FORAN, MD, ERNEST H. SHORE, MD, PHILLIP M. LEVIN, MD, *and* RICHARD L. TREIMAN, MD, *Los Angeles*

Long-term results with 52 bovine, 53 saphenous vein and 78 radial-cephalic arteriovenous fistulas (AVF) were analyzed. Side-to-end radial-cephalic AVF provided the best patency data, and remain the preferred access system for hemodialysis. Bovine AVF were next in ranking with better patency rates than for the saphenous vein AVF studied. Corrected one-year patency rates were 71 percent for bovine, 45 percent for saphenous and 91 percent for radial-cephalic AVF. The incidence of nonthrombotic complications with bovine AVF was higher than with saphenous vein AVF. Distal ischemia due to "steal" and certain bleeding and wound complications were unique to bovine AVF. Excellent dialysis blood flow rates and easy accessibility were provided by bovine grafts. When a satisfactory radial-cephalic AVF cannot be created, bovine graft AVF is an acceptable alternative for hemodialysis access.

NUMEROUS METHODS for providing vascular access for hemodialysis have been described during the past decade. Subcutaneous arteriovenous fistulas (AVF) of Brescia-Cimino type are now generally preferred for long-term dialysis access systems.[1,2] However, in patients whose forearm blood vessels are unsuitable for direct radial-cephalic arteriovenous anastomosis, other forms of AVF with an interposed bridge between artery and vein may be employed. Bridged-AVF systems are applicable in patients with peripheral arterial occlusive disease and those with small or damaged forearm veins.

Autogenous saphenous veins have been employed as bridged grafts for AVF since 1969. Early experiences with saphenous arteriovenous fistulas were favorable,[3-6] but long-term results have been less satisfactory[7,8] in addition to which many patients do not have suitable saphenous veins. In 1972, modified bovine arterial heterografts were recommended by Chinitz and coworkers as self-sealing prostheses in hemodialysis

From the Vascular Surgery Section, Department of Cardiac, Thoracic and Vascular Surgery, Cedars-Sinai Medical Center, Los Angeles.

Dr. Foran is Chief, Vascular Surgery Section, Cedars-Sinai Medical Center and Assistant Clinical Professor of Surgery, University of California, Los Angeles, School of Medicine; Drs. Shore and Treiman are Assistant Clinical Professors of Surgery, University of Southern California School of Medicine; and Dr. Levin is Assistant Clinical Professor of Surgery, University of California, Los Angeles, School of Medicine.

Submitted March 20, 1975.

This paper was presented at the Southern California Chapter of the American College of Surgeons at Santa Barbara in January 1975.

Reprint requests to: R. F. Foran, MD, 435 North Bedford Drive, Beverly Hills, CA 90210.

ABBREVIATIONS USED IN TEXT

AVF = arteriovenous fistulas
BOV = bovine grafts
RCAV = radial-cephalic arteriovenous
SAV = saphenous arteriovenous

access systems.[9] Encouraging short-term success with bovine arteriovenous fistulas also has been reported by others.[8,10-14] However, published long-term follow-up data have not been sufficient to permit comparison with alternative forms of AVF. This report reviews our experience with bovine grafts (BOV) for dialysis access, and compares this experience with that for radial-cephalic arteriovenous (RCAV) and saphenous arteriovenous (SAV) fistulas.

Clinical Material and Methods

Fifty-two BOV fistulas were constructed between April 30, 1972 and July 1, 1974.* Twenty-eight of these were done before January 1974 and have been observed for more than a year. The longest follow-up is 32 months. The remaining 24 BOV fistulas were created between December 1973 and July 1974, and all have been followed at least six months. None were lost to follow-up.

For comparison with the BOV fistulas, 53 SAV and 78 RCAV fistulas which were constructed between August 1971 and December 1973 were studied. All patients in these latter groups were followed for at least a year. Pertinent information regarding the three groups of patients is shown in Table 1.

The three groups of BOV, SAV and RCAV fistulas comprised 151 patients. Eighty were men and 71 women. All had chronic renal failure requiring maintenance hemodialysis. Eleven patients were diabetic. Patient ages ranged from 22 to 77 years, with a mean age of 52 years. Thirty-three patients were 65 years or older, constituting 22 percent of the total group. Dialysis was provided by means of percutaneous puncture of the fistulas two or three times each week. Thirty-two patients died and four had successful renal transplants during the follow-up period.

Selection of the particular form of AVF was not random, but was based upon evaluation of each patient's blood vessels and clinical status. Nonbridged AVF has been the system of choice for dialysis access, and therefore side-to-end RCAV fistula was constructed first whenever possible. Fifty-nine patients had only an RCAV fistula. SAV or BOV fistulas were created in patients whose blood vessels were inadequate for RCAV or when failure of other forms of fistula occurred. Twenty-nine SAV and 28 BOV fistulas were constructed as the primary form of access. Thirty-five patients had more than one type fistula during the period studied, and thereby provided data for more than one category.

TABLE 1.—*Clinical Data for Three Groups of Patients with Different Types of Arteriovenous Fistulas*

	RCAV	*SAV*	*BOV*
No. of patients	72	44	46
Women	32	23	24
Diabetics	3	5	5
Mean age, years	51	50	55
No. of arteriovenous fistulas	78	53	52
Deaths in follow-up	16	13	13
Deaths with patent AVF	9	11	11

AVF = arteriovenous fistulas RCAV = radial-cephalic arteriovenous
BOV = bovine grafts SAV = saphenous arteriovenous

The techniques of the operations have been described previously.[6-14] All RCAV anastomoses were side-to-end. In bridged-AVF systems, the arterial anastomoses were done end-of-graft to side-of-artery. Venous anastomoses were end-of-graft to either side-of-vein or end-of-vein. When antecubital veins were inadequate or damaged, grafts originating in the forearm were carried across the elbow for anastomoses to brachial veins. The bovine heterografts which were used had internal diameters of 6 to 8 mm.

Both straight and loop forms of SAV and BOV were constructed. Whenever possible, preference was given to straight configuration as originally described by Chinitz and co-workers. Locations included forearm, arm and anterior thigh. The distribution of the various bridged-AVF configurations which were constructed is shown in Table 2. Twenty-four BOV were in thigh locations, 26 in the forearm. All but one of the 53 SAV were placed in the forearm, 28 in straight and 24 in loop configuration.

Results

Patency Data. Nine spontaneous thromboses of BOV fistulas occurred. Of these, three fistulas were successfully maintained by thrombectomy and revision of anastomotic stenoses. Six could not be salvaged and required new dialysis access systems. Five BOV fistulas were surgically occluded

*The arterial graft (bovine) was obtained from Johnson & Johnson, New Brunswick, NJ.

TABLE 2.—*Distribution of Bridged Arteriovenous Fistula Locations and Configurations*

Configuration	*Location*	*Arterial Origin*	*Venous Insertion*	*No. SAV*	*No. BOV*
Straight	Forearm	Radial	Antecubital or brachial	23	17
	Arm	Brachial	Axillary	0	2
	Forearm	Brachial	Cephalic at wrist	5	2
	Thigh	Distal superficial femoral	Saphenous	0	16
Loop	Forearm	Brachial	Antecubital or brachial	24	7
	Thigh	Proximal femoral	Saphenous	1	8

BOV = bovine grafts SAV = saphenous arteriovenous

TABLE 3.—*One Year Patency Data for Radial-cephalic and Bridged Arteriovenous Fistulas*

	RCAV	*SAV*	*BOV*
Constructed at least one year before study	78	53	28
Patent on hemodialysis one year	62	19	17
Uncorrected patency rate	0.79	0.36	0.61
Excluded (patent at time of death or renal transplant)	10	11	4
At Risk one year	68	42	24
Corrected one-year patency, percent	91	45	71

BOV = bovine grafts RCAV = radial-cephalic arteriovenous SAV = saphenous arteriovenous

for treatment of complications of ischemia, bleeding and anastomotic disruption. Eight patients died with patent BOV. Thirty of the 52 BOV remain patent.

Mean survival time for all BOV fistulas was 13.7 months, with little variance for different locations or configurations.

Patency rates at one year are compared for the three forms of AVF in Table 3. Uncorrected one-year patency rates include as failures those patients with fistulas still functioning, who died or received successful renal transplants less than a year after the access procedure. More valid comparison is based upon a corrected one-year patency rate which includes only those fistulas which were actually at risk of occlusion for one year or more. Superiority of RCAV is clearly shown. Of the RCAV at risk, 91 percent remained patent at one year. Corrected one-year patency of BOV (71 percent) was definitely better than that of SAV fistulas (45 percent).

For SAV, little difference in patency was observed between straight and loop configurations. Thirty thrombotic occlusions of SAV fistulas occurred, three within one month and the rest within two years. Ten of 28 straight and 9 of 25 loop SAV were patent one year or longer. When only those SAV which were at risk one year are compared, the patency rate was 0.45 for each form. At two years, only 4 of 22 SAV fistulas remained patent. Mean survival time for all SAV fistulas was 11.2 months. Vein grafts which remained patent for long term were invariably 6 mm or greater in diameter. Mural hyperplasia with luminal stenosis caused most of the late SAV fistula failures, including some with veins of excellent caliber.

TABLE 4.—*Comparison of Patency of Saphenous (SAV) and Bovine (BOV) Arteriovenous Fistulas for Two Years After Construction*

	Months After Fistula Construction				
	3	6	12	18	24
Saphenous					
Patent/At Risk	37/49	30/48	19/42	14/40	4/22
Patency, Percent	76	63	45	35	18
Bovine					
Patent/At Risk	44/50	32/42	17/24	4/7	3/5
Patency, Percent	88	76	71	57	60

Table 4 compares corrected patency of all SAV and BOV at successive intervals of time. These data are shown graphically in Figure 1. The sharper initial decline of the SAV patency curve reflects the early failures of inadequate, small saphenous veins. After six months, the two curves assume somewhat more similar decline. Although only small numbers of BOV were at risk for 18 months (seven cases) and 24 months (five cases), patency remains above 50 percent.

Our initial bovine implants were straight femoral-saphenous grafts, and these fistulas have provided excellent long-term patency. However, despite our preference for the straight configura-

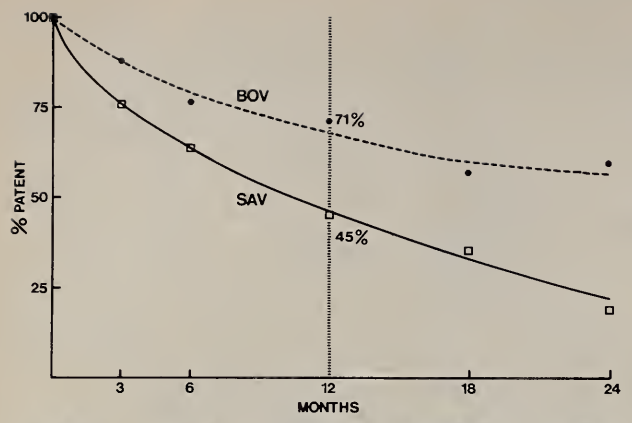


Figure 1.—Diagram comparing decrease in patency with time for bovine graft (BOV) and saphenous arteriovenous (SAV) fistulas.

tion, our data show that loop forms provided better patency at one year. All of the seven BOV loops at risk for one year have remained patent, regardless of location in arm or leg. Ten of 16 straight BOV (62 percent) were patent at one year.

Complications. Complications of BOV and SAV fistulas are listed in Table 5. Twenty-nine nonthrombotic BOV complications occurred. Eight of these, however, led directly to graft occlusion, either spontaneously or by surgical ligation.

Three patients had severe inflammatory reaction along the bovine graft tunnel, one of which persisted for several months and resembled a foreign body rejection phenomenon. This may have been due to insufficient washout of the preservative solution from the graft before implantation.

Bleeding complications occurred on three occasions when BOV puncture was performed earlier than seven days. In each instance, blood which extravasated from the needle puncture site dissected along the graft tunnel, producing tunnel hematomas and graft occlusion. In one patient, brisk external bleeding occurred through the six-day-old incision.

Ischemic complications due to fistula "steal" phenomena occurred with four of the 52 BOV fistulas. In one patient with severe peripheral arteriosclerosis, there was ischemic rest pain and loss of pedal pulses after a straight femoral-saphenous bovine fistula was constructed. Surgical ligation of the fistula produced relief of symptoms and return of distal pulses. Banding constriction of a forearm loop relieved hand ischemia in one patient, and spontaneous thrombotic occlusion accomplished the same result in another. The fourth patient has had no worsening of mild hand coolness and claudication noted immediately after creation of the fistula. We have not observed ischemic complications with any other form of dialysis access.

Early postoperative deaths include one patient who died 24 hours following construction of a BOV fistula in the thigh. Death occurred suddenly during hemodialysis carried out by means of a pre-existing Scribner shunt, and was due to ventricular arrhythmia. Another patient died one month after BOV fistula construction. She had extensive arteriosclerotic occlusive disease and a thrombotic propensity which precluded establishment of satisfactory vascular access for hemodialysis.

Late complications of BOV include one case of staphylococcal septicemia. Although no overt graft infection was apparent, the BOV fistula was a possible source of this sepsis, which resulted in death. No other deaths were related to the BOV fistula operations.

Late anastomotic disruption occurred in two patients, resulting in large false aneurysms with overlying skin necrosis. In one patient with a brachial artery to brachial vein BOV loop constructed in the forearm, two reoperations were done within 48 hours for correction of hand ischemia due to "steal." The venous anastomosis disrupted seven weeks later. The other patient had a profunda femoris artery-to-saphenous-vein BOV loop in the thigh. An abscess developed below the groin incision after 3½ months and responded to incision and drainage. Cultures repeatedly grew no organisms. Two months later (5½ months after construction of the BOV fistula), the arterial anastomosis disrupted, producing a rapidly expanding false aneurysm. Cultures

TABLE 5.—*Nonthrombotic Complications of Bridged Arteriovenous Fistulas*

	SAV	*BOV*
Early (within one month)		
Wound complication	0	3
Bleeding	0	3
Ischemia due to "steal"	0	4
Death	4	2
Late (after one month)		
Septicemia	3	1
Anastomotic disruption with false aneurysm and skin necrosis	0	2
Mid-graft false aneurysm	2	1
Graft infection	2	3
High output heart failure	0	1
Anastomotic stenosis	5	2

BOV = bovine grafts SAV = saphenous arteriovenous

taken at operation again showed no growth of microorganisms.

False aneurysms of mid-graft puncture sites were observed in one patient. This graft was not initially punctured until three weeks after surgical operation. Numerous pseudoaneurysms developed at puncture areas within one year.

Three infections involving bovine grafts occurred several months after operation, eventually resulting in occlusion of all three fistulas. Incision, drainage and removal of graft segments were required for eradication of these graft infections.

Only one instance of high output heart failure has been noted in our entire dialysis access experience. This was relieved by banding the patient's straight femoral-saphenous bovine graft. The fistula has continued to function satisfactorily for 21 months.

Impaired fistula blood flow due to anastomotic stenosis was corrected by surgical revision in two patients.

Discussion

From October 1964 to October 1974, the authors provided surgical access for hemodialysis in 611 patients at Cedars-Sinai Medical Center. A total of 1,411 Scribner shunt cannulations and 320 internal AVF of all types were constructed.[13] During the past four years, a side-to-end RCAV fistula has been our preference for dialysis access whenever feasible. Our initial enthusiasm for SAV fistulas as a suitable alternative was diminished by their high incidence of late occlusion. In 1972, we began constructing BOV fistulas for patients with failures of RCAV or SAV fistulas. Favorable experiences led to employment of bovine access systems for new patients whose blood vessels were inadequate for RCAV.

The present study documents the long-term superiority in patency of BOV over SAV fistulas. The 71 percent one-year patency rates obtained with BOV are quite acceptable, and are clearly better than with SAV. The blood flow rates provided for dialysis by BOV fistulas are excellent. Graft puncture for access to the circulation has been accomplished with relative ease in all patients. Operative morbidity for BOV procedures is definitely less than for SAV fistulas, since the tedious and not atraumatic vein removal is avoided. For forearm fistulas, the operation can be done entirely under local anesthetic.

We are in agreement with Payne and coworkers[8] regarding preference for placement of the graft in the thigh in a straight alignment, with arterial origin from the distal superficial femoral artery. However, our data suggest that loop forms in either leg or arm locations may provide higher patency rates.

The groin area has been long recognized as highly susceptible to postsurgical infection. Other locations for hemodialysis access should therefore be given careful consideration before selecting the groin, particularly for implantation of foreign body material such as bovine arterial grafts.

Despite our general satisfaction with BOV fistulas, a significant qualification is necessary. The incidence of complications was greater with BOV than with SAV, and certain complications were severe and difficult to manage. Of the 52 BOV fistulas studied, 10 early and 10 late nonthrombotic complications occurred. Six were serious: one bleeding problem, three cases of ischemia and two late anastomotic disruptions. Each of these posed a definite threat to the patient's life or limb, and five required urgent surgical occlusion of the BOV fistula.

Infections of BOV fistulas were usually more difficult than those seen with RCAV or SAV. Puncture site infections of RCAV and SAV generally responded well to systemic antibiotics, hot compresses and limited incision and drainage. Similar infections of BOV grafts were not eradicated as easily. Three graft infections led directly to thrombotic occlusion. Moreover, persisting infection of the occluded grafts required subsequent surgical drainage or graft removal, similar to experiences with synthetic prosthetic implants.

The development of multiple pseudoaneurysms in one bovine graft raises the possibility that this graft was defective. In addition, the three inflammatory wound complications associated with graft necrosis and the two instances of late anastomotic disruption may have been due to degenerative changes in the bovine grafts.

The ischemic complications seen with BOV fistulas can be prevented by appropriate measures during operation. It is essential that peripheral pulses be evaluated before surgery. Ischemia results from the high blood flow rates and the shunting of large volumes of blood through the BOV fistulas. Restriction of the size of the arterial orifice is the critical factor for controlling the volume shunted. After completion of the anastomoses but before releasing blood flow through the fistula, a known distal pulse is observed. The

quality of this pulse is then noted as the fistula is opened. If the pulse disappears, it is advisable to constrict the arterial end of the graft with a prosthetic band before wound closure. With this technique, we have avoided limb ischemia since our initial experiences with this complication.

The complication data reflect the presence of a few problem patients who had strong thrombotic tendencies or extremely poor vasculature for fistula construction. Four such patients in this study accounted for eight SAV and nine BOV complications, and all four eventually died. These deaths were related to our inability to provide satisfactory permanent vascular access for dialysis. No allowance has been made for the adverse influence of these patients upon the complication data.

The high death rate in this report (32 of 151 patients) reflects the relatively old age of our patient population and the high mortality associated with long-term hemodialysis.[15] Thirteen deaths occurred in both the BOV and SAV groups. Four deaths in the SAV group were attributed to SAV complications. Only two of the deaths in the BOV group were directly related to the fistulas. The death due to cardiac arrhythmia during dialysis 24 hours after operation must be regarded as a postoperative mortality. The death due to septicemia seven months after operation represents a late lethal complication.

A need remains for the reporting of larger numbers of one-year and two-year results with BOV fistulas. We hesitate to endorse BOV without qualification: the serious nature of certain complications which were encountered with BOV in this study requires a note of caution. We believe that the potential for serious or lethal complications is greater with bovine heterografts than with autogenous grafts. We still prefer an RCAV fistula for dialysis access in all patients when feasible. When an adequate RCAV cannot be established, consideration is given to an SAV fistula, provided the saphenous vein appears optimal. When these options do not exist, we prefer BOV fistula as an acceptable alternative for hemodialysis access.

REFERENCES

1. Byrne JP, Stevens LE, Weaver DH, et al: Advantages of surgical arteriovenous fistulas for hemodialysis. Arch Surg 102: 359-361, Apr 1971

2. External shunts and internal fistulas (Editorial). Ann Intern Med 74:1008-1009, Jun 1971

3. Flores-Izquierdo G, Ronces-Vivero R, Exaire E, et al: Autoinjerto venoso para hemodialysis (técnica original). Comunicación preliminar. Arch Inst Cardiol Mex 39:259-266, 1969

4. May J, Tiller D, Johnson J, et al: Saphenous-vein arteriovenous fistula in regular dialysis treatment. N Engl J Med 280: 770-771, Apr 3, 1969

5. Mozes M, Hurwich BJ, Adar R, et al: Arteriovenous vein graft for chronic hemodialysis—A preliminary report. Surgery 67:452-454, Mar 1970

6. Ehrenfeld WK, Grausz H, Wylie EJ: Subcutaneous arteriovenous fistulas for hemodialysis. Am J Surg 124:200-206, Aug 1972

7. Girardet RE, Hackett RE, Goodwin NJ, et al: Thirteen months experience with the saphenous vein graft arteriovenous fistula for maintenance hemodialysis. Trans Am Soc Artif Intern Organs 16:285-291, 1970

8. Payne JE, Chatterjee SN, Barbour BH, et al: Vascular access for chronic hemodialysis using modified bovine arterial graft arteriovenous fistula. Am J Surg 128:54-57, Jul 1974

9. Chinitz JL, Yokoyama T, Bower R, ét al: Self-sealing prosthesis for arteriovenous fistula in man. Trans Am Soc Artif Intern Organs 18:452-455, 1972

10. Haimov M, Burrows L, Baez A, et al: Alternatives for vascular access for hemodialysis—Experience with autogenous saphenous vein autografts and bovine heterografts. Surgery 75: 447-452, Mar 1974

11. Haimov M, Jacobson JH: Experience with the modified bovine arterial heterograft in peripheral vascular reconstruction and vascular access for hemodialysis. Ann Surg 180:291-295, Sep 1974

12. Zincke H, Hirsche BL, Amamoo DG, et al: The use of bovine carotid grafts for hemodialysis and hyperalimentation. Surg Gynecol Obstet 139:350-352, Sep 1974

13. Foran RF, Shore E, Levin PM, et al: Vascular access for hemodialysis, chap 17, *In* Massry SG, Sellers AL (Eds): Clinical Aspects of Uremia and Dialysis, 1st Ed. Springfield, Ill, Charles C Thomas, in Press

14. Johnson J, Kenoyer MR: Bovine graft arteriovenous fistulas for hemodialysis. Am J Surg 128:728-731, Dec 1974

15. Lindner A, Curtis K: Morbidity and mortality associated with long-term hemodialysis. Hosp Practice 9:143-150, Nov 1974

Refer to: Curreri PW, Marvin JA: Advances in the clinical care of burned patients (Medical Progress). West J Med 123: 275-281, Oct 1975

Medical PROGRESS

Advances in the Clinical Care of Burned Patients

P. WILLIAM CURRERI, MD, *and* JANET A. MARVIN, RN, MN, *Seattle*

Very few areas of medical science have experienced more rapid development of new and beneficial treatment approaches during the past two decades than the disciplines required for total care of patients with major thermal injury. The introduction of a multidisciplinary scientific approach to the diagnosis and treatment of very complex postburn complications has been primarily responsible for the major advances in clinical care. This report highlights those areas of advancement which have been most significant in upgrading current inpatient therapy.

THERMAL INJURIES constitute a major health problem in the United States today. Over 2 million people suffer burn injuries annually, of whom 70,000 must be admitted to hospital. The professional and paramedical requirements for the care of these patients are massive, since modern therapy demands the expertise of specially trained physicians, nurses, therapists, dieticians, social workers and psychologists. Thus, specialized burn units have been developed throughout the country to allow delivery of health care to seriously burned patients by integrated teams of clinical and research personnel. As a result rapid advances in patient care have been made during the past two decades resulting in notably improved survival and better postinjury function. Striking improvement has been achieved in six clinical areas including the evolvement of more physiological methods for fluid resuscitation; the development of new topical antibacterial agents for the control of burn wound sepsis; the increased availability and use of biological dressings (heterografts and homografts); improved operative techniques for removal of eschar and early autograft coverage; a more knowledgeable approach to the management of the metabolic response to thermal injury, and improved methods for preventing or correcting scar formation and limited mobility, once accepted as the sine qua non of burn injury.

From the Department of Surgery, University of Washington School of Medicine.

Dr. Curreri is the recipient of a Research Career Development Award from the National Institutes of Health.

Reprint requests to: P. W. Curreri, MD, Department of Surgery ZA-10, University of Washington School of Medicine, Seattle, WA 98104.

Fluid Resuscitation

Over the past twenty years, many resuscitation formulas have been developed as guides to the initial resuscitation of hypovolemic shock follow-

ing thermal injury. Most utilize various combinations of crystalloid and colloid solutions, but differ widely in the ratio of colloid to crystalloid, as well as the rate of fluid administration. The ideal resuscitation formula would rapidly restore normal hemodynamic stability. However, such a response is dependent upon the rate at which fluid is lost from the extracellular fluid compartment, the composition of the fluid lost and the ability of various solutions to restore an effective circulating and extracellular volume. Unfortunately most formulas have been derived empirically from clinical experience during which the amount of intravenous fluid required to restore renal function was accepted as optimal replacement therapy.

Although there still remains much controversy over "the solution" for the resuscitation of burn shock, certainly there is evidence to support the need for both crystalloid and colloid solutions. Almost two decades ago, Evans suggested the administration of 1 ml of colloid and 1 ml of an electrolyte solution per kg of body weight per percent total body surface area (TBSA) burned (up to 50 percent), and 2 liters of a nonelectrolyte solution to cover insensible water losses. Within a year the original Brooke formula appeared stressing the need for more electrolyte-containing solution and less colloid. Recent formulas have advocated even larger quantities of electrolyte solutions or use of hypertonic salt solutions. Proponents of hypertonic solutions cite limited edema formation, limited weight gain, a natural diuresis, preservation of gastrointestinal tract function and a decreased incidence of acute pulmonary edema as evidence for the superiority of their method.[1,2] Studies comparing hypertonic and hypotonic resuscitation regimes have failed to confirm the superiority of any one formula for reestablishing normal hemodynamic function within the first 24 hours. However, Baxter[3] has shown a prompt restoration of blood volume and cardiac output using a slightly hypotonic solution (lactated Ringer's) delivered at a rate that provides 4 ml per kg of body weight per percent TBSA burn. Although there may be occasional indications for the use of hypertonic salt solutions for the resuscitation of a patient with poor cardiac reserve, great care must be exercised in controlling the delivery rate of hypertonic saline, since too rapid administration may precipitate severe central nervous system disorders associated with plasma or cerebral spinal fluid hypernatremia.

The use of colloid for initial fluid resuscitation also remains controversial. The proponents of hypertonic therapy advise against the use of colloid, while the revised Brooke formula still advocates its desirability, although in even smaller quantities than the original Brooke formula. The Baxter formula advocates the use of a small volume of plasma only after completion of crystalloid resuscitation, that is, during the second 24 hours. At least two investigators[3,4] have been unable to show any better restoration of plasma volume following the administration of colloid during the first 24 hours than after the administration of electrolyte solutions alone. In the second 24 hours, however, plasma volume can be more easily maintained in patients with greater than 40 percent TBSA burns by the infusion of small amounts of plasma (500 to 2,000 ml). Presumably the larger molecules in plasma are better retained within the partially repaired capillaries resulting in increased intravascular oncotic pressure.

Data from numerous studies[5] now suggest that both volume and the sodium ion are critical to providing adequate resuscitation, resulting in early expansion of depleted plasma and extracellular fluid volumes and return of the cardiac output to normal. After 24 hours colloid remains the most effective solution to maintain plasma volume without further increasing edema formation. Baxter's formula has been derived to provide specific replacement of known deficits measured by simultaneous determinations of red cell volume, plasma volume, extracellular fluid volume and cardiac output during burn shock—and therefore it remains the standard against which new formulas must be compared. The Baxter formula advocates the administration of 4 ml of lactated Ringer's solution per kg of body weight per percent of body surface area burned, during the first 24 hours postinjury. Fluid therapy during the second 24 hours, according to this formula, consists of the administration of free water (D5W) in quantities sufficient to maintain the serum sodium at 140 mEq per liter (approximately 4 to 5 liters in a 70 kg man with a 50 percent burn) and plasma sufficient to return the plasma volume to normal and sustain adequate signs of resuscitation (approximately 250 ml for each 10 percent TBSA burn over 20 percent). Potassium replacement is required to replace the increased urinary losses associated with both the resuscitation and the subsequent catabolic state.

During the first 24 hours the rate of fluid ad-

ministration is adjusted to correspond as closely as possible with the rate of extracellular fluid loss. Findings in Baxter's studies[3] have confirmed that extracellular deficits occur rapidly within the first 6 to 12 hours postinjury. Therefore half of the total calculated fluid volume is delivered during the first 8 hours and the remaining fluids more slowly over the next 16 hours.

The adequacy of resuscitation can best be judged by frequent measurements of vital signs, central venous pressure and hourly urine output, and observation of general mental and physical response. Urine output still remains one of the most reliable guides to adequacy of fluid therapy. Acute tubular necroses, with resultant renal failure, is extremely rare in an adequately resuscitated patient with the possible exception of a patient in whom there is extensive muscle damage (such as in electrical burn) resulting in hemochromagen release and intratubular protein precipitation. Therefore oliguria during the early postburn period is most often an indication of inadequate resuscitation, with increased fluid administration the treatment of choice. Restriction of fluid is almost never indicated and the administration of diuretics should be reserved for those cases in which tubular damage from circulating pigments appears likely. Osmotic diuretics (for example, mannitol) probably should be used prophylactically in this group of patients, but only after a sufficient amount of resuscitation fluids have been administered.

Antibacterial Therapy

The second major advancement in the improvement of overall burn mortality has been the development of topical therapy to control burn wound infection. Monafo and Moyer[6] initially advocated modern antibacterial topical therapy using aqueous silver nitrate in the early 1960's. This method of therapy employs the use of 0.5 percent silver nitrate solution as a continuous wet soak in combination with large bulky dressings. The mode of action of silver nitrate is not specifically known, but is probably dependent upon the free silver ion, which is active at relatively low concentrations. This drug is effective against most Gram positive organisms and most strains of Pseudomonas, although it has limited effectiveness against other Gram negative bacteria such as Enterobacter, Aerobacter and Klebsiella. It is most effective on the surface of the wound, but has limited penetration of deeper tissues—and therefore in third degree burns the eschar must be removed rapidly to prevent colonization of the underlying tissue. The major complication associated with the use of silver nitrate solution is severe electrolyte depletion (primarily sodium and chloride), and therefore frequent monitoring of serum electrolytes and specific replacement therapy is required. Silver nitrate therapy has been acclaimed to be the most economical topical agent since the drug itself is inexpensive and available in most hospital pharmacies. However, the large quantities of dressings required, the increased staff requirements to adequately carry out the therapy and the phenomenal housekeeping problems add to the cost of the therapy. In addition, the necessity for bulky dressings inhibits the early active movement of extremities and therefore encourages less than optimum joint function.

In the mid-1960's, Moncrief and Lindberg[7] introduced mafenide acetate (Sulfamylon®), a topically applied cream that allowed open treatment of burn wounds. Mafenide acetate has proven effective against a wide range of Gram positive and Gram negative organisms as well as most anaerobes. This drug actively diffuses through the eschar, thus providing protection in the depths of the eschar at the interface between viable and nonviable tissue. In the open technique of treatment, this drug allows frequent, careful examination of the wounds, facilitates the treatment of associated injuries and allows intensive physical therapy—therefore improving joint mobility. Unfortunately, the drug is a potent inhibitor of carbonic anhydrase which may produce acid-base derangements, particularly in the presence of pulmonary dysfunction. Its use is associated with a pronounced reduction of the buffering capacity of the blood as a result of increased bicarbonate excretion by the kidney, and simultaneous hypocarbia as a result of hyperventilation. Other disadvantages associated with the use of this drug have been pain on application, an occasional hypersensitivity reaction (5 to 7 percent) to the sulfa drug, delayed eschar separation due to improved bacterial control and the emergence of opportunistic infections—including Providencia, Serratia, fungal, yeast and viral infections.

Silver sulfadiazine (Silvadene®), developed by Fox[8] in the late 1960's, has shown great promise. It has essentially the same bacterial spectrum as mafenide acetate, but has fewer disadvantages. The major disadvantages are the hypersensitivity reaction to sulfa drugs (5 to 7 percent), delayed

eschar separation and emergence of opportunistic infections. Silver sulfadiazine appears to desiccate the wound less than other agents and consequently keeps the eschar soft, allowing for much greater joint mobility. It does not inhibit carbonic anhydrase activity, and its application is soothing rather than painful.

Betadine ointment, a water soluble topical antiseptic complex of polyvinylpyrrolidone-iodine, is effective against a wide range of Gram positive and Gram negative organisms and some fungi. This drug readily diffuses through the eschar and is absorbed and excreted rapidly with no observed systemic toxicity. Although it only recently has been used for topical therapy of burns, early observations indicate that the agent rapidly desiccates the eschar even when used under light dressings. In addition, its application is painful to patients with superficial (second degree) wounds. As with other topical agents, emergence of opportunistic infections after prolonged use of this agent should be expected.

Bacterial colonization of the burn wound may be accurately monitored by making serial quantitative wound biopsy cultures as described by Pruitt[9] and Loebl.[10] Surface cultures from the wound are misleading, since they are notably influenced by environmental bacterial flora. In addition they fail to measure bacterial proliferation in the depths of the eschar where invasion of viable tissue by microorganisms will occur causing a highly lethal septicemia. On the other hand wound biopsy cultures yield quantitative data allowing early alteration in therapy when bacterial proliferation has escaped control of the topical agent employed.

Although topical agents have reduced the incidence of bacterial invasion of viable subeschar tissue with subsequent burn wound sepsis, bacterial proliferation may still escape the control of all currently used topical chemotherapeutic agents. Administration of antibiotics by needle clysis beneath the eschar has been employed with success in such situations. Teplitz[11] first described decreased vascularity of the burn wound and underlying subcutaneous tissues during the first few weeks postburn. The sparse capillary blood supply in the wound results in inadequate wound delivery of sufficient concentrations of systemic antibiotics for effective *in vivo* bacterial control. Life-threatening bacterial colonization, which develops despite the use of topical chemotherapy may be effectively treated by the delivery of an appropriate antibiotic directly into the subeschar tissue. This therapy is most effective when initiated at the time that wound colonization reaches 10^4 to 10^5 organisms per gram of tissue, as determined by quantitative wound biopsy culture techniques. Antibiotics used should be selected after review of *in vitro* organism sensitivity. The entire daily "systemic" dose of the selected antibiotic should be dissolved in a solution of isotonic saline or half-strength saline of sufficient quantity to cover each 44 square centimeter area of burn eschar with 25 ml of solution once daily.

Biological Dressings

The use of biological dressings in the form of homograft (cadaver skin) and heterograft (porcine skin) has greatly enhanced wound care. Major advantages offered by biological wound dressings include restoration of the water vapor barrier (in this way decreasing evaporative losses), protection of the wound from trauma and infection, reduction of pain and improved joint function. Improvement of subsequent autograft take is also noted since hypermaturation of granulation tissue is prevented and graft bed receptability is tested before definitive autografting. For most purposes homografts or heterografts can be used interchangeably.

Biological skin dressings may be used on superficial second degree wounds immediately postburn to reduce pain, prevent wound infection and stimulate more rapid wound epithelialization. However, physicians must ensure that partial thickness burns treated in such a manner are indeed superficial and that all loose skin and debris have been debrided before heterograft application. The grafts must be inspected at 24 hours. If adherent, the heterograft should be left in place until reepithelialization has taken place and spontaneous separation occurs. If the heterograft is not adherent, the grafts must be removed and topical chemotherapeutic agents should be applied to the burn in the conventional manner. Biological skin dressings may also be used to decrease pain, promote epithelialization and protect epithelial buds from traumatic damage after deep partial thickness burn injury—providing application of the heterograft is delayed for one to two weeks, during which time wound bacterial proliferation is controlled with topical chemotherapeutic agents and necrotic debris is removed by daily debridement.

In a patient with full thickness burn wounds

(third degree), the application of biological wound dressings may serve several purposes. They may be employed to aid in the debridement of the last small pieces of fibrous material remaining on the wound after conventional debridement. Heterograft application accelerates debridement by encouraging bacterial lysis of the few remaining dermal elements. Obviously application of heterograft or homograft under such circumstances must be used with caution if systemic sepsis is to be avoided. In general, no more than 5 to 10 percent of the body surface area should be treated in this manner at any one time, and the granulation bed must be debrided as thoroughly as possible before graft application. When biological dressings are used on the granulating beds of full thickness wounds, they should be examined daily for any areas of suppuration, and changed daily if this occurs. If the grafts adhere to the granulating surfaces they must be changed at least every 3 to 5 days until autografting is accomplished. Finally, homograft has recently been used at a number of centers for temporary wound coverage (3 to 6 weeks) in patients undergoing wound excision after massive burn injury, allowing time to develop sufficient donor sites in other areas of spontaneously healing partial thickness burn.

Operative Techniques

Several major advances in operative technique have been developed over the past decade. Tanner mesh (expanded) grafts to cover large areas from limited donor sites are now widely used except on face, hands, feet and flexion creases. Several approaches to early primary excision of necrotic tissue have also been reexamined in patients with major burns (>60 percent). Although the use of topical therapy for wound bacterial control has been associated with improved survival in patients with burns of less than 60 percent, no significant increase in survival has been observed in massively burned patients. Consequently, there recently has been renewed interest in methods for accomplishing early rapid debridement of the burn wound and early wound closure in order to prevent life-threatening complications (such as sepsis, malnutrition) following burn injury. Current methods for rapid eschar removal include enzymatic debridement, tangential debridement, cold knife debridement and laser excision.

Proponents[12-14] of enzymatic and tangential excision point to two major advantages of both methods of debridement. They may be accomplished with minimal loss of viable tissue and avoidance of general anesthesia during the early postburn period. Each of these techniques has serious disadvantages. The effectiveness of currently available enzymatic agents has been seriously questioned by several investigators. Although theoretically topical enzyme use should not be associated with damage of viable tissue, conversion of wounds from partial thickness to full thickness may be observed if they are used indiscriminately. Because most of the agents require wet dressings to be activated and may also interfere with the antibacterial effectiveness of topical chemotherapeutic agents, the prolonged use of such enzymes may actually increase the potential risk of burn wound sepsis. If these agents are to be used at all, they should be used over small areas (<10 percent TBSA) and only for a period of 72 hours postinjury. In addition, the wounds should be inspected frequently for signs of wound infection or invasive sepsis.

Tangential debridement, first popularized in Czechoslovakia, allows controlled rapid debridement by shaving the eschar in layers with a dermatone or free hand knife over a period of several days. Because the debridement is controlled by the surgeon, sacrifice of viable tissue is minimized and blood loss reduced. The technique is less valuable when used for debridement of full thickness burns since it results in exposure of viable subcutaneous fat before the development of granulation tissue. The exposed, relatively avascular fat is predisposed to secondary infection unless homografts are immediately applied and adherence of the graft obtained. Homograft failures on such unprepared beds are unfortunately common.

Cold knife excision allows eschar removal over 20 to 30 percent TBSA with minimal operative time. A major advantage of this method is that a surgeon can select the level of the excision. Excision to fascia usually allows immediate successful application of homograft with semipermanent survival (one to four months), thus accomplishing wound coverage while available donor sites are recropped. However, the procedure is accompanied by massive blood loss even when deliberate hypotensive anesthesia is used.

Carbon dioxide (CO_2) laser excision, the newest technique used for eschar removal, has proven to be more effective in reducing operative blood loss. This technique employs a CO_2 laser

to both cut through the tissue and to coagulate small vessels that have been transected. However, operative time is prolonged due to the relatively low laser energy source employed. In addition, required equipment is expensive (approximately $20,000), cumbersome and requires the use of special eye protection equipment for the staff. Recently Hishimoto[15] has suggested slower wound healing and poor graft acceptance following laser excision as a result of damage to previously viable tissue in the recipient bed as a result of energy absorption during the excision.

Excisional therapy requires the consideration of several special requirements. These procedures should be accomplished early in the burn course while bacterial colonization is below 10^4 organisms per gram of tissue. The authors prefer to prophylactically administer a single preoperative infusion of subeschar antibiotics into the area to be excised in order to reduce the number of viable bacteria. An unlimited supply of banked or fresh homograft and adequate amounts of stored and fresh blood should be available for use. In the case of cold knife excision the anesthesiologist should be experienced with techniques of deliberate hypotensive anesthesia.

Nutrition

The acute postburn period is characterized by hypermetabolism, negative nitrogen balance and rapid weight loss. Although much research over the past decade has been aimed at defining the cause of the hypermetabolic response to thermal trauma, relatively little is known about the exact etiological mechanism. Wilmore[16] has recently shown that the increased metabolic rate in these maximally stressed patients is related to an increased production of catecholamines. Elevated levels of epinephrine and norepinephrine provide a hormonal environment which favors substrate mobilization and increased energy use associated with accelerated excretion of urinary nitrogen and loss of body weight. Further studies by Wilmore[17] have suggested that the hypermetabolic response is a consequence of homeostatic readjustment within the hypothalamus which occurs following injury. Burn patients appear to reset their thermal regulatory set point upward, thus increasing the discharge of sympathetic impulses to stimulate heat production and substrate mobilization in order to maintain a new and elevated core temperature.

To meet the increased energy demands brought about by the altered metabolic rate, extremely large quantities of carbohydrates and proteins are necessary to prevent weight loss and promote anabolic recovery. Preinjury dietary habits often limit the oral intake of sufficient nutrients. In addition, frequent occurrences of mental confusion and ileus associated with sepsis and other hypovolemic states, as well as frequent operative procedures, often limit oral alimentation during the first postburn month. Therefore a combined enteral-parenteral dietary program is often necessary to maintain positive caloric and nitrogen balance in these patients. Curreri[18,19] and Wilmore[20] have shown that up to 8,000 kilocalories per day can be administered without significant hyperosmolar changes by a combination of enteral and parenteral fluids. Curreri and his associates[21] have derived a formula for predicting caloric requirements which minimizes weight losses in adult burned patients. The formula, based on preburn body weight and burn size, was derived from observed measurements of caloric intake and body weight changes during the course of burn therapy. The formula advocates the intake of 25 kilocalories per kg of body weight plus 40 kilocalories per percent burn per day. This may be accomplished in most patients by a combination of regular oral dietary intake plus continuous tube feedings to augment the diet. When sufficient caloric support cannot be maintained by enteral feeding, then intravenous hyperalimentation may be necessary for optimal caloric support. Although septic complications may be associated with the administration of intravenous hyperalimentation solutions, with meticulous care in preparation and administration of solutions, as well as strict aseptic catheter care and frequent changes of the catheter site (every three days), this risk can be minimized. A dietary program which is designed to accomplish positive energy balance and weight stabilization is the only known means of preventing nutritional deterioration in severely hypermetabolic patients. Failure to provide adequate caloric and nitrogen intake often results in poor wound healing, weight loss, organ failure and pulmonary sepsis.

Rehabilitation

Postburn contractures and the development of hypertrophic scars are the two principal chronic complications associated with thermal injury. Often the disability associated with these wound

healing abnormalities has been accepted as inevitable. Despite meticulous attention to all aspects of wound care, a physician is occasionally confronted with a viable patient, who has little will to live because of the disfigurement and deformity caused by hypertrophic scars and joint contractures. Preventive therapy must be started immediately after the burn injury and continued for six months to a year after the initial injury. Active movement of joints through a complete range of motion in both burned and unburned areas must be accomplished several times a day. Such physical therapy should be begun during the first 24 hours postinjury and should be supervised by trained therapists and nursing personnel. Splinting and positioning with especially designed devices is particularly important in the prevention and treatment of contractures of limbs and neck. Larson and his associates[22] have reported reduction of hypertrophic scar formation with the application during the convalescent period of conforming isoprene splints or elastic dressings (Jobst® stockings) or both which exert pressure on the scar causing better alignment of collagen fibrils and reduction of local interstitial edema. Such splints and elastic dressings should be employed following hospital discharge for a period of at least six months in order to discourage delayed development of hypertrophic scar. If at all possible surgical correction of contractures should be postponed until scar maturation has occurred, usually 12 months or more after wound closure. Before this time, operative release of joint contractures should generally be limited to those which severely impair self-care activities, compromise joint function or impede skeletal development.

REFERENCES

1. Monafo WW: Treatment of burn shock by the intravenous and oral administration of hypertonic lactated saline solution. J Trauma 10:575, 1970
2. Caldwell FP, Cusali RE, Flanigan WJ, et al: What constitutes the proper solution for resuscitation of the severely burned patient? Am J Surg 122:655, 1971
3. Baxter CR, Shires GT: Early resuscitation of patients with burns, Vol IV, *In* Welch CE (Ed): Advances in Surgery, Vol IV. Year Book Medical Publishers, Chicago, 1970, pp 308-324
4. Pruitt BA, Moylan JA: Current management of thermal burns. Adv Surg 6:237-288, 1970
5. Moylan JA, Mason AD, Rogers PW, et al: Postburn shock: A critical evaluation of resuscitation. J Trauma 4:354-358, 1973
6. Monafo WW, Moyer CA: Effectiveness of dilute aqueous silver nitrate in the treatment of major burns. Arch Surg 91:200, 1965
7. Moncrief JA, Lindberg RB, Switzer WE, et al: The use of a topical sulfonamide in the control of burn wound sepsis. J Trauma 6:407, 1966
8. Fox CL Jr, Rappole BW, Stanford W, et al: Control of pseudomonas infection in burns by silver sulfadiazine. Surg Gyn & Obstet 128:1021, 1969
9. Pruitt BA, Foley FD: The use of biopsies in burn patient care. Surg 6:887-897, 1973
10. Loebl EC, Marvin JA, Heck EL, et al: The use of quantitative biopsy cultures in bacteriologic monitoring of burn patients. J Surg Res 16:1-5, 1974
11. Teplitz C, Davis P, Mason AD, et al: Pseudomonas burn wound sepsis I pathogenesis of experimental pseudomonas burn wound sepsis. J Surg Res 4:200, 1964
12. Pennisi VR, Capozzi A, Friedman G: Travase, an effective enzyme for burn debridement. Plast Reconstr Surg 51:371-376, 1973
13. Monafo WW, Aulenbacher CE, Pappalardo C: Early tangential excision of the eschars of major burns. Arch Surg 104:503-508, 1972
14. Janzekovic Z, *In* Dergane M (Ed): Present Clinical Aspect of Burns: A Symposium, (Maribor, Yugoslavia: CP Marborski tisk, 1968), pp 99-112, 215-230
15. Hishimoto K, Rockwell RJ, Epstein RA, et al: Laser wound healing compared with other surgical modalities. Burns: J Intn'l Soc Burn Injuries 1:13-22, Sep 1974
16. Wilmore DW: Nutrition and metabolism following thermal injury, *In* Moncrief JA (Ed): Clinics In Plastic Surgery, Vol I. Philadelphia, Pa, WB Saunders, 1974, pp 603-619
17. Wilmore DW, Orcutt TW, Mason AD, et al: Alterations in hypothalamic function following thermal injury. (In press)
18. Curreri PW: Long-term supranormal caloric dietary programs in extensively burned patients, *In* Cowan C, Scheets W (Eds): Intravenous Hyperalimentation. Philadelphia, Lea and Febiger, 1972, pp 137-141
19. Wilmore DW, Curreri PW, Spitzer KW, et al: Supranormal dietary intake in thermally injured hypermetabolic patients. Surg Gynec Obstet 132:881-886, 1971
20. Curreri PW, Wilmore DW, Mason AD, et al: Intracelluar cation alterations following major trauma, effect of supranormal caloric intake. J Trauma 5:390-396, 1971
21. Curreri PW, Richmond D, Marvin JA, et al: Dietary requirements of patients with major burns. J Am Dietet Assoc 65: 415, 1974
22. Larson DL, Abston S, Evans EB, et al: Techniques for decreasing scar formation and contractures in the burned patient. J Trauma 11:807, 1971

Specialty Conference

Participants
IVAN HARWOOD, MD
NANCY OLMSTED, MD
RICHARD RABENS, MD
ELAINE MISCHLER, MD
MICHAEL WELLER, MD
WILLIAM L. NYHAN, MD, PhD

From the Departments of Pediatrics and Radiology, University of California, San Diego, School of Medicine, and University Hospital, San Diego

Refer to: Harwood I, Olmsted N, Rabens R, et al: Croup and epiglottitis—University of California, San Diego, and University Hospital, San Diego (Specialty Conference). West J Med 123:282-289, Oct 1975

Croup and Epiglottitis

WILLIAM L. NYHAN, MD, PH D:* *The management of croup is an interesting and often provocative aspect of pediatric practice. We shall present two illustrative cases. The first will be presented by Dr. Rabens.*

RICHARD RABENS, MD:† The first patient presented at Mercy Hospital with dyspnea and stridor. He was a 3½-year-old Mexican-American boy who was well until one week before admission, when a nonspecific febrile illness developed accompanied by malaise. The whole family had the same illness. The patient improved in a few days and was well until two days before admission, when low-grade fever recurred. He was treated with one baby aspirin every four hours. On the day before admission, there continued to be a slight fever and a raspy, barking cough developed. The patient began to experience difficulty in breathing on the night before admission. The mother described the difficulty as "heavy breathing" which prevented him from sleeping well that night.

On the morning of admission the patient began retracting and grunting. He was brought to the Emergency Room at Mercy Hospital. The admitting officer noted the child to be tachypneic and to have stridor and intercostal retractions. The epiglottis was looked for specifically by the examiner but was not seen. The child was given 0.2 ml of epinephrine subcutaneously and intermittent positive-pressure breathing (IPPB) treatment with isoproterenol hydrochloride (Isuprel®) without any improvement. On an x-ray film of the chest, bilateral patchy infiltrates in both lower lobes and in the right upper lobe were seen. The child was admitted to the Pediatric Service. The history was unremarkable except for an episode of bronchitis several months previously.

On physical examination, the patient was found to be well developed and in acute respiratory distress. Inspiratory stridor and very pronounced substernal retractions were noted. A barking cough was prominent. The temperature was 101.2°F (38.4°C), the pulse 160 and respiratory rate 40 per minute, and the blood pressure 112/74 mm of mercury. There was no cyanosis. Findings on examination of the ears, eyes and nose were normal. Diffuse rhonchi were heard over the chest without wheezing. The rest of the examination gave findings within normal limits.

Laboratory studies showed a leukocyte count of 18,800 per cu mm with 76 percent segmented

*Professor and Chairman, Department of Pediatrics.
†Resident in Pediatrics.
Reprint requests to: William L. Nyhan, MD, PhD, Department of Pediatrics, University Hospital, P.O. Box 3548, San Diego, CA 92103.

cells, 4 percent band forms, 15 percent lymphocytes and 5 percent monocytes. The hemoglobin was 12.2 grams per 100 ml. Results of urinalysis and analysis of the blood for electrolytes and blood urea nitrogen (BUN) were normal. On a lateral x-ray film of the neck, some narrowing of the subglottic air column was seen. The examination in the oral pharynx was deliberately deferred and otolaryngological consultation was obtained. An intravenous infusion was started and maintenance fluids provided. Blood culture was obtained and ampicillin was given intravenously in a dose of 100 mg per kg of body weight per day. The child was put in a cool mist tent and given racemic epinephrine by mask. The anesthesiologist on call was advised of the patient's presence. The consulting otolaryngologist examined the child by indirect laryngoscopy and made a diagnosis of laryngotracheobronchitis. He felt that tracheostomy was not indicated. The child's breathing remained extremely difficult during the first few hours in the hospital, although there was slight improvement after each treatment with racemic epinephrine. The patient still required racemic epinephrine every hour for the first few treatments and then every two hours. Treatment was begun with hydrocortisone sodium succinate (Solu-Cortef®) in a dose of 2 mg per kg of body weight every six hours. There was gradual improvement through the night. By the next morning he was breathing with only moderate retractions, and he gradually improved over the next three days. Findings on an x-ray study made on the day of discharge, the fourth hospital day, showed improvement in the areas of infiltration noted originally, and the tracheal air column was not narrow.

QUESTION FROM THE AUDIENCE: *How did he tolerate the treatment with racemic epinephrine?*

DR. RABENS: He tolerated it. This patient did not struggle against it at all. He was an exhausted child. The House Staff was very worried that the child might be in too much respiratory distress. There was argument back and forth as to whether a tracheostomy should be done.

QUESTION FROM THE AUDIENCE: *How much steroid did the patient receive?*

DR. RABENS: He got, I believe, about 50 mg.

DR. NYHAN: *The second patient will be presented by Dr. Mischler.*

ELAINE MISCHLER, MD:* Our second patient was a two-year-old boy who was admitted to University Hospital with a chief complaint of respiratory difficulty. He had been well except for an episode of abdominal pain the night before admission until 11 o'clock on the morning of the day of admission when he was noted to be lethargic. There was decreased appetite and a temperature of 105°F (40.6°C) had developed. The patient was seen in the emergency room at 5 pm and found to have bilateral otitis media. At that time there was no inspiratory stridor. He was given prescriptions for penicillin, sulfisoxazole (Gantrisin®) and Dimetapp® and sent home. At 11 pm he was brought back to the emergency room because of inspiratory stridor. At that time, a temperature of 103°F (39.4°C) was present. The mother reported that this difficulty in breathing had developed during a period of approximately one hour. The patient was admitted with a diagnosis of probable acute epiglottitis. The history was otherwise noncontributory.

On admission the vital signs included a pulse of 150 and respirations of 24 per minute. Respirations were labored, and there was inspiratory stridor and pronounced substernal retractions. The temperature was 102°F (38.9°C). The child sat leaning forward. He had a very anxious appearance, and it was very impressive to watch him breathe. He was not cyanotic. There were dull tympanic membranes bilaterally and shotty cervical adenopathy. The lungs were clear, and findings on cardiac examination were normal. The rest of the physical examination gave entirely normal findings.

Laboratory data showed a leukocyte count of 20,900 per cu mm with 72 percent segmented cells, 17 percent band forms, 9 percent lymphocytes and 2 percent monocytes. The hematocrit was 37. The serum concentrations of electrolytes, the BUN and the urinalysis were all within normal limits.

It was decided to defer examination of the epiglottis until the child could be taken to the operating room, so that if a tracheostomy was needed, it could be done under controlled conditions. The child was given racemic epinephrine by nebulizer with no improvement. Intravenous

*Chief Resident in Pediatrics.

ampicillin was begun in a dose of 200 mg per kg of body weight. Mild hyperaeration was noted on an x-ray film of the chest. On a lateral x-ray study of the neck, there was questionable glottic and subglottic edema. The child had just arrived in the operating room when he became completely obstructed. Intubation was carried out. Then a tracheostomy was placed. We looked at the epiglottis after the tracheostomy, and it was erythematous and about four times normal in size. Subsequently the child's throat culture grew out Hemophilus influenzae.

The hospital course was uneventful. The tracheostomy tube was removed after five days.

DR. NYHAN: *If there are no questions we shall turn to Dr. Weller for evaluation of the roentgenological features of this problem.*

MICHAEL WELLER, MD:* Radiography of the neck requires proper positioning in order to make the diagnosis of croup or epiglottitis or both. The neck must be fully extended. If the films are done upright, the chin must be elevated and the head well back. If the films are done supine, the shoulders must be elevated so that the head drops back enough to get a cross table lateral film which shows the neck in full extension. This is the position of maximal airway caliber. Most children will not resist this positioning. The arms must be pulled down toward the feet, either by a parent or suitable restraints, in order for the subglottic airway to be seen in the lateral view.

It is always worthwhile to review the normal anatomy of the oropharynx and larynx before launching any discussion of croup or epiglottitis. Examining the neck in the lateral projection, one can usually see air in the valleculae, which are small depressions formed by the medial and lateral glossoepiglottic folds. These are located just above the body of the hyoid bone in the lateral view. Extending from the valleculae, a soft tissue shadow, finger-like in configuration, is noted which is the free margin of the epiglottis. From the free margin of the epiglottis, the aryepiglottic folds sweep downward posteriorly, and show a concave posterior configuration. Where they meet the posterior pharyngeal wall is a mound of soft tissue representing the arytenoid cartilages. A small oval lucency just anterior to the arytenoid cartilages represents the laryngeal ventricle. Bands of soft tissue density above and below the laryngeal ventricle represent the false and true vocal cords, respectively. The subglottic tracheal airway begins at the bottom of the true cords. In the lateral view, mild anterior buckling of the subglottic airway is a normal variation, which can be eliminated by further extension of the neck. In the anteroposterior projection, lateral paired air-containing structures are the pyriform sinuses. The inferior limit of the pyriform sinuses usually localizes the level of the true vocal cords. From this point downward, the trachea begins as the subglottic airway. In the anteroposterior projection the subglottic airway, from the under surface of the true cords, usually has a rounded shoulder and has been likened to the configuration of a gothic arch.

The typical radiologic signs of croup are those of subglottic narrowing of the trachea in both the anteroposterior and lateral projections (Figure 1). Because of the peculiar laxity of the mucosa and lack of adherence of mucosa to the submucosa in the proximal few centimeters of the subglottic trachea, this area develops the most severe edema with acute infectious croup. In the anteroposterior view, this edema produces airway narrowing, obliterating the normal subglottic gothic arch configuration. The airway then takes on a much more tapered appearance, similar to a sharpened pencil, or byzantine arch. In the lateral view, both decreased caliber and decreased radiolucency of the subglottic area, because of diminished air in the lumen of the trachea at this level, are noted.

The radiologic differential diagnosis of croup includes subglottic hemangioma, but the history is usually quite different. Subglottic hemangiomas usually do not present with an acute onset, but rather with symptoms soon after birth. Other differential diagnostic possibilities include an aryepiglottic cyst or edema from a nonopaque foreign body.

A child with epiglottitis presents a somewhat different picture. The lateral view of the neck is the single most important projection for the diagnosis of epiglottitis (Figure 2). As the edema of the epiglottis becomes pronounced, the valleculae are obliterated. The normal finger-like epiglottis becomes hugely swollen and the aryepiglottic folds become either straight or convex posteriorly, compared with the normal concave posterior configuration.

It is important to remember that children with

*Associate Adjunct Professor of Radiology.

Figure 1.—Left, croup, lateral neck radiograph. The single arrows indicate subglottic narrowing. Note the normal epiglottis (double arrows) and laryngeal ventricle (broad arrow). **Right,** croup, anteroposterior neck radiograph. (Same patient in both left and right figures.) The single arrows indicate the inferior limit of the pyriform sinuses, which also corresponds to the level of the true cords. Subglottic narrowing is present (open arrows). Note the normal buckling of the trachea to the right.

Figure 2.—Epiglottitis. Lateral neck radiograph. The epiglottis is swollen (arrow) and has lost its normal finger-like configuration (compare with Figure 1, Left). The subglottic airway is normal.

epiglottitis may have croup also. Neck films in both the anteroposterior and lateral projections should be done whenever upper airway obstruction of any kind is suspected. It is my feeling that in any child with croup or epiglottitis, lateral films of the neck ought to be made before direct visualization of the epiglottis is attempted. However, this is with the understanding that the child should come to the x-ray department with a physician in attendance, who should be prepared to carry out emergency intubation if necessary. Films obtained on the second patient presented showed classic epiglottitis.

Dr. Nyhan: I agree with Dr. Weller on the subject of carrying out x-ray studies in a patient with croup. It is especially a problem because these emergencies often occur in the middle of the night. The other point we should reiterate is that the physician going with the patient should bring the appropriate equipment so that he can do something if something happens. Another comment is that these roentgenographic distinctions look easy when Dr. Weller provides his usual beautiful demonstration. We can all see these things clearly when he points them out to us. It is much more difficult in the middle of the night. The physician may need not only a good position on the film, but he may need an expert like Dr. Weller in order to read them.

Our next speaker will be Dr. Nancy Olmsted.

Nancy Olmsted, md:* There are four possible sites of obstruction in the upper airway: at the level of the epiglottis, at the level of the vestibular folds, at the level of the larynx and in the subglottic area. The two levels that are of concern to us today are the epiglottis and the subglottic region. The vestibular folds may become involved with chemical inhalations and foreign bodies, and the larynx may be an important site of cysts or laryngeal paralysis. In epiglottitis, the course is usually of sudden onset with high fever in a toxic patient. Such a patient may present with a wide open mouth, the tongue sticking out, and drooling. There may be dysphagia. The patient is very sick. In this disorder the inflammation is not limited to the epiglottis. It may also involve the aryepiglottic folds so that edema is present both anteriorly and posteriorly.

In croup, the swelling is most prominent in the

*Fellow in Pediatric Pulmonary Disease.

subglottic area. This is in the region of the cricoid cartilage. It is the smallest part of the airway in childhood. This is the region that limits the size of an endotracheal tube. In general, croup has a slower onset and less fever than epiglottitis. It is usually caused by a virus. Parainfluenza viruses are commonly found in patients with croup. Very severe croup has been associated with influenza A virus. The disorder can be caused by a number of other viruses, including respiratory syncytial virus and occasionally enteroviruses such as echo and Coxsackie. It is important to remember that laryngeal croup can be caused by diphtheria. The characteristic presentation is of a very toxic child with a history of no immunizations.

DR. NYHAN: *We shall turn now to Dr. Harwood for consideration of the management of these problems.*

IVAN HARWOOD, MD:* The two patients presented in this conference were classic examples, the first of viral croup and the second of Hemophilus influenzae epiglottitis. These clinical syndromes are well known. I would like to discuss some of the more controversial aspects of diagnosis and treatment. There has been considerable recent literature, particularly on newer methods of diagnosis and treatment, and much of it is contradictory. When a child presents with a severe croup syndrome, inspiratory stridor, cough, hoarseness and signs of obstruction, a critical consideration is the cause—is it viral or is it bacterial (that is, due to Hemophilus influenzae). The reasons are the therapeutic implications. In 11,400 cases of viral croup as tabulated by Adair,[1] an average of 5 percent required a tracheostomy. The range was 0 to 13 percent. In smaller groups of patients with epiglottitis due to H influenzae, 70 to 100 percent required an artificial airway. In these patients, obstruction developed so severe that intervention was required and usually tracheostomy. Perhaps more important is the rapidity and capriciousness of this disease process. As illustrated in the second case, complete obstruction may appear very rapidly. It often has a way of happening when and where you least expect it. These are the reasons for making an unequivocal diagnosis in a patient with a severe croup syndrome.

There are three principal ways in which to differentiate these two entities. The first of these is clinical. A judgment can often be made from the history, appearance and response to initial therapy. The danger in relying on the clinical presentation is that epiglottitis may not present with the classical picture. Nevertheless, the patient may go on and follow the usual fulminant course while the patient is in the x-ray department, in the elevator or in a croup tent on the ward. The second way is by x-ray. Dr. Weller has illustrated that x-ray examination can be diagnostic. Two dangers deserve emphasis. The first is that the patient may obstruct while x-ray studies are being made. The positioning, manipulation and restraints that are necessary to get the films may promote obstruction. We have discussed the importance of having the proper personnel and equipment in the x-ray suite. The second problem is that films may not be of sufficient quality for technical reasons, particularly when done in the middle of the night, to permit a diagnosis. Possibly a combination of technical difficulties and inexperience of the person looking at the x-ray films may be why this method does not invariably provide the diagnosis. Visual inspection is the third approach to definitive diagnosis. The short oral pharynx of a younger child and an epiglottis that may be two to four to six times normal size, make it almost always possible to visualize the epiglottis by simple inspection. This is without any instrumentation in about 30 percent of the patients and with quick gentle pressure with a tongue blade in the rest of the patients. If a large cherry-red colored epiglottis is seen, it surely must be one of the most certain diagnoses in pediatrics.

The dangers of visual inspection are also two. First, visualization may be inadequate. This is related more to the skill and determination of the examiner than to variations in the anatomy. The second problem is a danger that is discussed every time this technique is brought up, that of precipitating a respiratory arrest by the manipulation involved in looking, particularly with a tongue blade. In a review of 103 cases of H influenzae epiglottitis, Baxter,[2] at the Montreal General Hospital, came to the conclusion that this is not an important consideration. The epiglottis and aryepiglottic folds are so swollen and so rigid in the later stages of the disease that a wait of five minutes, a few drops of saliva into the vallecula or a change in position can precipitate obstruction. In this disease, later sometimes means minutes. In other words, the child who is

*Assistant Professor of Pediatrics.

going to obstruct with a quick look and by one deep pass of the tongue blade is likely to obstruct two minutes later with nothing else being done. If this is the case, it should be contrived that the inevitable intubation occurs under optimal circumstance. Where these circumstances are obtained depend on the institution and the personnel and equipment available, and it will vary from institution to institution. Generally, the place should be the operating room, the emergency room or the intensive care unit. Access to all of the necessary tracheal intubation equipment should be insured including a rigid pediatric bronchoscope. Personnel involved should be a pediatrician, an otolaryngologist and an anesthesiologist. Once a diagnosis of epiglottitis is made, a tracheostomy should be done. I do not personally believe in waiting for medical therapy to take effect. The odds are just too strongly against its effectiveness. The available data support the idea that once the diagnosis is made, a tracheostomy should follow promptly.

Another controversy that comes up at this point is whether to use a nasotracheal tube or a tracheostomy. Intubation is almost always going to last more than 24 hours. My own feeling is that there are too many complications of prolonged intubation with upper airway disease for nasotracheal intubation to be an acceptable method of management. Downes[3] has reviewed the use of nasotracheal tubes in patients with croup. In 18 patients with upper airway obstruction treated with nasotracheal tubes, there were severe late complications in 11. There were two deaths and three patients with late tracheal stenosis. This probably occurs because of a foreign body (the tube) in an area that is intensely inflamed. If a patient is obstructed enough to require an airway, the opening may be pinpoint. To provide an adequate airway, you must use a hard tube that compresses the delicate, inflamed tissue.

Let us consider the other group of patients. If the diagnosis is not epiglottitis by history, inspection and x-ray examination, then it is probably viral croup or laryngotracheobronchitis. The mainstay of therapy in this disease has become nebulized racemic epinephrine. It is usually given in a dose of ½ ml in 3½ ml of saline and delivered by IPPB for 10 to 15 minutes, usually by mask. It may be repeated as required. The limitation on how often this therapy can be repeated is tachycardia, which is not often seen with this drug. Proper use is important. The drug has to be delivered to the target organ. Wafting a gentle mist of epinephrine over the child's face does not get any of the drug into the inflamed area. Initially it is often necessary to hold a struggling, sick child with a mask clamped on his face and the inspiratory time on the respirator set so that there is a long inspiratory time to insure adequate delivery of the drug. Some of the problems encountered in using this regimen have been related to a lack of aggressiveness in clamping the mask tightly to the face. The treatment works by local effect. Vasoconstriction can shrink inflamed mucous membranes. Systemic epinephrine should not be employed, as it has no effect on subglottic edema. It may increase the oxygen requirement of the child, and in someone who may be at the compensation point, an increase in oxygen requirement may trigger respiratory failure. A mist tent is probably of no real value. It may be dangerous because when a child is wet, he loses heat which increases the oxygen requirement. For the doctor there may be a loss of visual contact with the patient in the tent. Oxygen is employed only in an emergency. A patient with croup who is cyanotic is in respiratory failure. The use of steroids remains controversial.

In viral croup or in epiglottitis, a child may arrest under less than ideal conditions, in a place where the tools for definitive therapy are not at hand. The child can no longer breathe or is about to arrest and is cyanotic. My first choice of a way to handle the situation is to employ an oral tracheal tube. I use the Cole tube because it has a shoulder. It narrows down to the small portion of the tube that actually goes into the airway. The tube is stiffer than other tubes and has a sharper bevel. One does not need wire or other mechanical devices in the tube to stiffen it. A tube should be used that is approximately half the size that would normally be chosen for a particular child. The aim is to provide an emergency airway that will be adequate until the child can be provided with a tracheostomy. If this cannot be accomplished in about 30 to 60 seconds, then a cricothyroid puncture is mandatory. There is no such thing as an emergency tracheostomy. It takes too long. It is also an extremely hazardous procedure if it is done under less than controlled circumstances. On the other hand a cricothyroid membrane puncture is easy. The landmarks are easy to identify. If you feel the thyroid cartilage, the Adam's apple, then right below it is the

cricoid ring, and as you put your finger from one to the other there is a space between the two. This is the place to make the hole. It can be made with a trocar, a pen knife or scalpel. The usual technique is to take the blade of the scalpel and make a horizontal puncture in the cricothyroid membrane and then take the handle of the scalpel, put it in and turn it vertically providing an opening through which the child can breathe.

These considerations raise the question of needles. Needles are not adequate to provide an airway for a child. An easy way to prove this is to get some 15 gauge needles, two or three even, put them in your mouth and try to breathe through them. It is not possible to move enough air through them. It is important to forget about needles, look at the anatomy book and feel the landmarks on one's own neck or somebody else's until one knows where the cricothryoid membrane is and then to be prepared mentally to puncture it if the situation demands.

Summing up the management of severe croup, first of all, have a plan that is tailored for each institution or each situation and have it available and well known by all of those who may be involved in first-line care. Second, epiglottitis should be suspected in any child that is croupy. Third, a visual inspection should be made under optimal circumstances. If the epiglottis appears to be normal or cannot be seen, then x-ray studies should be done. If a cherry-red colored epiglottis is seen, the patient should be taken directly to the operating room, or whether tracheostomy is done. In dealing with this problem, the pediatrician should always be mentally prepared for the worst.

QUESTION FROM THE AUDIENCE: *How often does a child need a tracheostomy on the second attack of croup?*

DR. HARWOOD: I do not think that a second attack is necessarily an indication for tracheostomy. It has not been tabulated in series and reported. Adair has listed all of the large published reports on viral croup and tracheostomy and mortality. We have more recently received a letter from him in response to an article that reported that patients with croup did not respond to racemic epinephrine, and in his experience no patient treated with racemic epinephrine has required tracheostomy in approxihately 500 patients over the last seven years.

QUESTION FROM THE AUDIENCE: *How many times do you use racemic epinephrine?*

DR. HARWOOD: If we restrict our experience to viral croup, not epiglottitis, we expect an immediate response, but the airway obstruction may recur. Then we repeat it as often as necessary. Tachycardia is the limiting side effect. In a patient with very severe viral croup that responds to racemic epinephrine, it is reasonable to give a 10 minute treatment and 15 to 20 minutes later to give another treatment for 5 or 10 minutes.

QUESTION FROM THE AUDIENCE: *Do blood gas determinations help in the management of croup?*

DR. HARWOOD: Yes, they do. If you find desaturation, that means physiological hypoventilation; if a patient is cyanotic, there is going to be an elevated carbon dioxide level, and this means respiratory failure. Most of the time when a child is cyanotic things are happening very quickly, and if a patient is desaturated, you know it. The other relevant problem is a patient with long drawn out viral croup. The patient may be getting tired and very gradually begin hypoventilating. This type of patient may fool you clinically, and blood gases may be very helpful in that situation, more so than in an acute emergency.

QUESTION FROM THE AUDIENCE: *Once you have seen the epiglottis, why get an x-ray film?*

DR. HARWOOD: It is not necessary in epiglottitis. But if the epiglottis is normal, there may be something in there, such as a foreign body. There may be a cyst or a tumor. If there is another abnormality, the patient is more likely to develop a croup syndrome. I think it is reasonable to get an x-ray film on the first episode of croup in any child. It is not necessary in a patient with repeated episodes of croup.

QUESTION FROM THE AUDIENCE: *Do you admit all patients you treat with racemic epinephrine?*

DR. HARWOOD: There are differences of opinion. Adair has said that he uses racemic epinephrine on outpatients. He gives them racemic epinephrine, and if they get better, he sends them home. I would not recommend that. I think that anyone sick enough to require racemic epinephrine should be in the hospital.

DR. NYHAN: *Something that has been bothering me you alluded to earlier. Dr. James Cherry has recently reported in* Pediatrics[4] *what looked to me like a controlled study on racemic epinephrine and as I remember reading it, he could not tell the control from the treated. Do you have a comment on that study?*

DR. HARWOOD: Yes. The controlled part of that study involved twenty patients. The number seemed to me to be inadequate. He did not state whether patients that did poorly and did not respond to racemic epinephrine had epiglottitis. There was no information as to which disease entity he was treating. This was what prompted the questionnaire from Dr. Adair. He was inquiring about experience in treating epiglottitis, and he did not expect them to respond.

QUESTION FROM THE AUDIENCE: *Would you treat a patient with epiglottitis with ampicillin?*

DR. HARWOOD: I believe that epiglottitis is caused by Hemophilus influenzae. Today the drugs of choice are ampicillin and chloramphenicol.

REFERENCES

1. Adair JC, Ring WH, Jordan WS, et al: Ten year experience with IPPB in the treatment of acute laryngotracheobronchitis. Anesth Analg (Cleve) 50:649-654, 1971

2. Baxter JD: Acute epiglottitis in children. Laryngoscope 77: 1358-1367, 1967

3. Striker TW, Stool S, Downes JJ: Prolonged nasotracheal intubation in infants and children. Arch Otolaryngol 85:210-213, 1967

4. Gardner HG, Powell KR, Roden VJ, et al: The evaluation of racemic epinephrine in the treatment of infectious croup. Pediatrics 52:52-55, 1973

Repeated Taps vs. Craniotomy for Subdural Hematomas

For a number of years neurologists interested in this particular field have questioned the value of craniotomy and the extensive use of surgical procedures recommended in the past and stemming largely from the experience of neurosurgeons . . . The operation itself, which is a very extensive and traumatic operation, cannot possibly remove all the membranous material and clotted blood that make up a chronic subdural hematoma. One can achieve as much by multiple aspirations of fluid from the subdural space, carrying out a subdural tap whenever there is a sign of increased pressure, such as fullness of the fontanelle or vomiting or the sudden onset of fever to suggest that enough fluid has accumulated to justify another tap. And so we now have two schools of thought—the original one consisting of the craniotomy and the second one consisting of tapping repeatedly until fluid is no longer attained. The group advocating the repeated taps will admit that a certain percentage of children will continue to show fluid with repeated tapping and that this is finally treated by setting up or establishing a shunt from the subdural space so that fluid will continually discharge from this space until the brain expands to fill the space and fluid formation comes to an end. I personally think that the data that are accumulating in this particular field strongly suggest that repeated tapping is as successful, if not more so, than the craniotomy and I believe that more and more neurosurgeons are being won over to the medical (if you can call it medical) approach with repeated taps than by extensive use of surgical operation.

—SYDNEY S. GELLIS, MD, *Boston*

Extracted from *Audio-Digest Pediatrics*, Vol. 20, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, California 90057.

Refer to: Pancreatic diarrheal syndromes—Medical Staff Conference, University of California, San Francisco. West J Med 123:290-296, Oct 1975

Pancreatic Diarrheal Syndromes

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask each chief medical resident to speak at Medical Grand Rounds at the end of his year in this capacity. We are most appreciative of the leadership that Dr. Hayden Klaeveman has brought to this position. He has had a continuing interest in the subject of gastrointestinal hormones and will review for us today the diarrheal syndromes associated with disorders of the pancreatic islet cells.*

DR. KLAEVEMAN:† In 1958 Verner and Morrison described two cases of profuse intractable watery diarrhea associated with severe hypokalemia in a noninsulin-secreting islet cell tumor of the pancreas.[1] In the first reported patients, in contrast to patients with the Zollinger-Ellison syndrome, achlorhydria was present, leading to the acronym WDHA syndrome (standing for watery diarrhea, hypokalemia and achlorhydria). In the 17 years since this initial report, some 50 patients with this devastating disorder have been described and in the ensuing years it has become apparent that achlorhydria is not necessarily an integral part of the syndrome. In fact, in most patients there is normal or decreased gastric acid secretion leading to application of the term "pancreatic cholera" to this syndrome. Considered in terms of hormonally mediated pancreatic disorders, these patients represent approximately 5 percent of nonbeta islet cell tumors of the pancreas.

The outstanding feature in these patients is diarrhea of variable severity and duration, generally of a progressive nature. In most patients, the symptoms have been present for three to four years before diagnosis. In its fulminant form, the diarrheal stool has the appearance of weak tea and contains little formed substance, while in the more quiescent form the stools take on a mushy consistency. The stool is inoffensive and there is no blood present. Abdominal cramping is sometimes present while weight loss is inevitably seen. Nausea and vomiting may occur in the more fulminant episodes.

As the diarrhea progresses, symptoms due to hypokalemia and dehydration appear. The patient may complain of generalized muscle weakness and even paralysis, and may even show signs of impending stupor.

During the attacks the serum potassium concentration frequently is less than 2 mEq per liter

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Hayden Klaeveman, MD, Chief Resident.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
AMP = adenosine monophosphate
APUD = amine precursor uptake, decarboxylation
G17 = heptadecapeptide gastrin
GLI = enteroglucagon
GIP = gastric inhibitory polypeptide
MEA = multiple endocrine adenomatosis
MSH = melanocyte-stimulating hormone
PGE_1 = prostaglandin type E_1
VIP = vasoactive intestinal polypeptide
WDHA = watery diarrhea, hypokalemia and achlorhydria
ZES = Zollinger-Ellison syndrome

and is always less than 3 mEq per liter. Fecal water losses average 5 liters per day and fecal potassium losses are 200 to 400 mEq per day during attacks. Loss of bicarbonate leads to the features of hypokalemic acidosis. Azotemia results from dehydration and hypokalemic nephropathy.

In general, findings on roentgenographic studies, stool cultures, sigmoidoscopy, stool fat determinations and urinary 5-HIAA (hydroxyindoleacetic acid) concentration studies are normal. Steatorrhea, if present, is mild.

Gastric acid secretion ranges from normal to histamine-fast achlorhydria. Peptic ulcer disease is not a feature of this syndrome.

There are other interesting and unusual features of this syndrome.

- Decreased glucose tolerance with or without overt diabetes mellitus occurs in approximately 50 percent of patients. Glucose metabolism frequently returns to normal after successful tumor resection. It has not been established whether the tumor secretes a hormone with hyperglycemic actions or whether the improved tolerance is due to correction of hypokalemia.
- Hypercalcemia occurs in approximately 50 percent of the patients and, like the impaired glucose tolerance, it may be abolished by tumor resection. In one series of four patients in whom hypercalcemia and watery diarrhea syndrome were present, parathyroid adenoma was shown in only one patient, and the true frequency of hyperparathyroidism is probably much less than this. Multiple endocrine adenomatosis syndromes are unusual in these patients. Consequently, neck exploration in these patients should be postponed until the effect of resection of the pancreatic tumor on calcium metabolism can be assessed.
- Cutaneous flushing of head and neck has been observed in approximately 20 percent of patients with the syndrome and again has resolved with successful tumor resection. There has been no other evidence of carcinoid syndrome and no evidence of abnormal metabolism of serotonin, or other vasoactive amines.

Other less frequently observed aberrations have included: gallbladder disease with stones in six patients, an enlarged gallbladder filled with dilute bile rich in bicarbonate and chloride in several patients.

The diagnosis should be suspected in patients with documented chronic watery diarrhea, hypochlorhydria and hypokalemia in whom the carcinoid syndrome, small and large bowel lesions (for example, villous adenomas), malabsorption of bile salts or nutrients or both, bacterial and parasitic infections, extrapancreatic neoplasms (for example, medullary carcinoma of the thyroid) and laxative abuse have been excluded. Pancreatic scanning and celiac arteriography have been of little help in delineating the tumor.

The treatment is primarily surgical with either extirpation of the tumor or, if the pancreas appears normal, diagnostic distal pancreatectomy, as 80 percent of the lesions are in the body and tail of the pancreas. If this is not curative and microscopic study shows diffuse hyperplasia, only total pancreatectomy is curative in the absence of metastatic disease.

In 53 reported cases to date, 30 percent of patients have been cured by removal of a benign tumor. In another 13 percent of these patients the diagnosis was not suspected antemortem, and at postmorten examination all had surgically resectable benign tumor. Diffuse hyperplasia was present in 20 percent, and in 8 of 11 patients, or 73 percent of these, surgical resection was curative. In 37 percent of these patients, malignant tumors with metastases were present, and only two patients benefitted from surgical operation. Therefore, 75 percent of patients with WDHA syndrome have been, or could have been, cured by surgical procedures.[2]

It is for those unfortunate patients with metastatic disease that other modes of therapy are required. One patient has been cured by radio-

therapy, and the administration of adrenocorticosteroids has afforded temporary relief in others (however, steroid therapy may lead to release of gastric secretory inhibition with resultant peptic ulceration).

Of chemotherapeutic regimens, one patient has been successfully treated with 5-fluorouracil. Most recently two patients with metastatic islet cell tumors have been treated with the antitumor antibiotic streptozotocin which is selectively toxic to pancreatic islet cells by inhibition of pyridine nucleotide synthesis. In both patients, there has been a salutory response to therapy (for 12 and 13 months respectively) after intra-arterial administration of the drug. It remains to be seen whether this remission will be maintained.[3]

Next I would like to turn to a consideration of the etiologic agent in this syndrome. The cell line which gives rise to these tumors appears to be that of the APUD (amine precursor uptake, decarboxylation) cells which constitute an endocrine system in the epithelium of the gastrointestinal tract, pancreas, bile ducts and bronchi. The embryologic origin of these cells is unclear—some hold that the APUD cells are of entodermal (foregut) origin, whereas others propose that they derived from neural crest tissue and therefore are neuroendocrine in origin.

In addition to serotonin, APUD cells synthesize polypeptide hormones, including gastrin, secretin, glucagon, vasoactive intestinal polypeptide (VIP), enteroglucagon (GLI) and probably other hormones. Because the WDHA syndrome is associated with APUD cell proliferation it might be expected that cell proliferation in organs other than the pancreas might give rise to the syndrome. This is supported by a recent report on four patients with bronchogenic carcinoma in whom WDHA was associated with an increased plasma VIP concentration.[4]

Of the candidate hormones which might produce this syndrome, the leading culprit is VIP followed by secretin and then gastric inhibitory polypeptide (GIP). Of 30 patients with the disorder studied by Said, in 25 there were increased plasma levels of VIP.[4] Bloom and associates have reported increased concentration of this peptide in plasma, tumor, or both, in another six patients with WDHA.[5] On the other hand, Kraft and Zollinger have been the major proponents of the secretin hypothesis, which is based on early observations by Gardner that both secretin and extracts of WDHA tumors caused inhibition of water and electrolyte transport *in vitro*. These authors have observed secretin-like activity in sera from certain patients with pancreatic cholera.[6] However, several studies have failed to show increased pancreatic water and bicarbonate secretion in patients with pancreatic cholera.

VIP and secretin have certain structural similarities, sharing 9 of 28 amino acids in common. Furthermore, virtually every tissue which responds to secretin responds in a similar fashion to VIP.

Actions of VIP include vasodilation (flushing), inhibition of histamine and pentagastrin stimulated acid secretion (achlorhydria), stimulation of electrolyte and water secretion by the pancreas, gallbladder relaxation (dilated gallbladder), stimulation of small intestinal secretion and stimulation of glycogenolysis (abnormal glucose tolerance test). Animal studies have shown that VIP, like prostaglandin type E_1 (PGE_1) and cholera toxin, stimulates small bowel adenylate cyclase, increases intracellular cyclic adenosine monophosphate (AMP), and produces net secretion of fluid and electrolytes in isolated ileal mucosa. Furthermore, VIP, but not secretin, stimulates human small intestinal adenylate cyclase.[7]

However, in the two patients reported by the group at the National Institutes of Health, increased activity of adenylate cyclase was not found in small bowel biopsy studies, nor were increased serum VIP concentrations, but intracellular cyclic AMP was not measured.

Lastly, Elias and co-workers have reported one patient with WDHA in whom positive immunofluorescence was noted in a tumor when an antisera against GIP was used.[8]

To summarize, the etiologic agents in WDHA syndrome are as yet unidentified. The leading candidate is VIP, but in several patients an increase in VIP concentrations in plasma was not found. There are at least two possible explanations for this: (1) Except for gastrin, radioimmunoassays for gastrointestinal hormones are not widely available or are poorly standardized; (2) since the APUD cell system produces a gamut of potential culprits, more than one hormone might produce the same clinical constellation.

Zollinger-Ellison Syndrome

In the time remaining, I will briefly discuss the other hormonally mediated pancreatic diarrheogenic syndrome. The syndrome of fulminant peptic ulcer disease with recurrences despite repeated

gastric operations, gastric hypersecretion and nonbeta islet cell tumors of the pancreas was first described in 1945, but it was Zollinger and Ellison in 1955 who first suggested that a hormone from the tumor was responsible for the disease.[9] It has now been established beyond reasonable doubt that the polypeptide gastrointestinal hormone gastrin is present in abundant quantities in the tumors and in the circulation of patients with the Zollinger-Ellison syndrome (ZES) and that the pathophysiologic events that characterize the Zollinger-Ellison syndrome represent consequences of excess circulating gastrin. It has been proposed that in analogy to insulin-containing insulinomas the term "gastrinoma" be applied to the tumors.[10]

Clinical Manifestations

- *Incidence.* The true incidence of ZES has not been established, nor is the true frequency of Zollinger-Ellison tumors among patients with peptic ulcer disease known. At present, there are more than 1,000 reported cases. It is probable that gastrinomas are present in less than 1 percent of patients with the diagnosis of peptic ulcer disease.
- *Age and sex.* The reported age range for patients with ZES is from 7 years to 90 years with a mean age of onset between the third and fifth decade of life. Sixty percent of the patients are male, although there is probably no sexual predominance.
- *Symptoms.* Abdominal pain is the most common presenting complaint, being present in 70 to 95 percent of patients. The location and quality of pain may be similar to that of uncomplicated peptic ulcer disease, or may be severe and relentless. By the time of diagnosis, symptoms have been present in most patients for more than one year.

In their review of 260 cases, Ellison and Wilson reported that in 93 percent of patients, peptic ulcer disease was present and in 7 percent, diarrhea without peptic ulceration was present.[11] They reported pain related to peptic ulcer disease in 74 percent, pain related to diarrhea in 15 percent, pain related to perforation in 18 percent, melena in 22 percent, hematemesis in 19 percent, diarrhea in 36 percent and vomiting in 26 percent.

Diarrhea has been reported in a third to three quarters of patients with ZES, and is responsive to treatment by gastric aspiration, as well as by total gastrectomy. The diarrhea is due principally to the presence of excess gastric acid secreted into the upper gastrointestinal tract. In addition, pentagastrin has been shown to reduce the absorption of water in the human proximal small intestine. However, since correction of acid hypersecretion by aspiration or gastrectomy corrects the diarrhea, it is unlikely that the direct hormonal effects of gastrin are major factors responsible for diarrhea.

Abnormal small bowel morphology has been described in patients with ZES, including gastrin metaplasia, submucosal edema and hemorrhage, abnormal villi and cellular infiltration of the lamina propria. Rapid transit is a common radiologic finding in patients with ZES, but the mechanism is unknown.

In summary, the diarrhea of Zollinger-Ellison syndrome is caused by multiple factors, including (1) delivery of excess acid to the duodenum, (2) damage to the small bowel mucosa by gastric acid, (3) decreased small bowel absorption resulting from the action of gastrin and from mucosal damage and (4) hypermotility.

Steatorrhea is frequently found in patients with ZES. However, the precise frequency of this abnormality has not been established. Steatorrhea is a consequence of irreversible inactivation of pancreatic lipase at low duodenal pH and precipitation of glycine conjugated bile salts at acid pH —thus decreasing their availability for micelle formation.

In 10 to 40 percent of patients with Zollinger-Ellison syndrome, there are associated nonpancreatic endocrine tumors, being termed multiple endocrine adenomatosis (MEA) type I or Wermer's syndrome. Hyperparathyroidism is the most commonly associated endocrine abnormality. Pituitary, adrenal, thyroid and ovarian tumors are less common.

In a review by Ballard of patients with type I MEA, parathyroid abnormalities were present in 88 percent, with pancreatic and pituitary abnormalities in 85 and 65 percent respectively. A 19 percent incidence of adrenal and thyroid disorders was found.[12]

Rarely an islet cell tumor may produce multiple hormones, such as adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), glucagon and insulin.

It has been observed in several patients that correction of hyperparathyroidism by resection of one or more adenomas notably improved symptoms of peptic ulcer disease, and decreased gastric acid secretion when ZES was also present.

Pathology

Immunohistochemical techniques have been successful in demonstrating gastrin in islet cells of the normal pancreas. Gastrin-containing granules have been localized to cells found in the periphery of the pancreatic islets. These cells have staining characteristics of delta cells. Of interest, although the highest concentration of immunoreactive gastrin is found in the gastric antrum, to date only one case of a gastrinoma of the stomach has been reported. The majority of gastrinomas are located in the pancreas or duodenum.

Recently Polak and co-workers have proposed the possible existence of two types of Zollinger-Ellison syndrome. In patients with ZES type I, there are notably elevated serum gastrin levels with antral gastrin cell hyperplasia. Such patients tend to be young, and tend to have a relatively short history of peptic ulcer disease when compared with patients with the "usual" type II ZES with gastrinomas.[13]

Physical Examination

There are no diagnostic physical findings in Zollinger-Ellison syndrome. Patients may show weight loss, epigastric tenderness and signs of hypermotility. Tumor masses are rarely palpable.

X-ray Studies

Findings on barium studies of the upper gastrointestinal tract are almost always abnormal. It has been suggested that the diagnosis of Zollinger-Ellison syndrome is primarily the radiologist's responsibility.

Radiographic examination of the stomach frequently shows excess gastric juice in the stomach and large gastric folds due to mucosal hyperplasia. Occasionally a large atonic stomach and rarely an isolated gastric ulcer is found.

The most common abnormality of the duodenum, seen in approximately 75 percent of patients with Zollinger-Ellison syndrome, is an ulcer in the duodenal bulb or immediate postbulbar area. Other duodenal findings include evidence of duodenitis with blunted valvulae conniventes, and irregularity of the duodenal wall, with dilation of the duodenal lumen.

The radiographic findings in the jejunum are similar to those in the duodenum. The presence of distal duodenal or proximal jejunal ulcers is highly suggestive of Zollinger-Ellison syndrome, but occur only in approximately 22 percent of cases.

Angiography has been useful in showing pancreatic lesions, but is positive in less than a third of cases. Similarly, success in showing gastrinomas with selenomethionine scanning has been low.

Gastric Secretion

The principal laboratory finding which suggests the diagnosis of Zollinger-Ellison syndrome is gastric acid hypersecretion, especially in the basal state. The two measurements of acid secretion which appear to give the best indication of ZES are the rate of basal acid secretion and the ratio of basal to peak stimulated acid secretion, or acid concentration.

The criteria applied to basal acid secretion in patients with intact stomachs are: (1) Twelve-hour overnight secretion of greater than 100 mEq of hydrochloric acid (HCl), and (2) one-hour basal secretion of greater than 15 mEq of HCl.

Ellison and Wilson reported 74 percent of patients with ZES secreted greater than 100 mEq of HCl overnight. However, 3 percent of patients with peptic ulcer disease secreted acid at this rate, and a third of patients with ZES failed to meet this criterion.

The ratio of basal to peak stimulated acid secretion (BAO:MAO) of greater than 0.6 has been found in approximately 60 percent of patients with ZES. However, there are reports of up to 15 percent of normals who have ratios of greater than 0.6.

Measurements of acid secretion in the stomachs of patients after operation may produce varied results due to variable recovery of acid and contamination by alkaline reflux from the upper small intestine. It has been suggested that greater than 5 mEq per hour of acid secretion in a patient with previous acid reducing operations should suggest the diagnosis of ZES.

Identification of gastric acid hypersecretion in a patient with peptic ulcer disease now requires serum gastrin measurement by radioimmunoassay to establish the diagnosis of ZES.

Gastrin

Time does not permit a review of the gastrin story which has recently been reviewed. Briefly, several forms of immunoreactive gastrin have been identified.

- There is heptadecapeptide gastrin (G17), which exists in two forms, gastrin I and gastrin II. Gastrin II has a sulfate on the tyrosyl residue in

position 12. The C-terminal tetrapeptide amide possesses the full range of biologic activity of the heptadecapeptide amide.

This form of gastrin predominates in human antral mucosa and in gastrinomas, has a half life of approximately five minutes, and has a greater molar potency than other forms of gastrin. Gastrin is also present in the intestine which has a gradient of concentration with highest values in the proximal duodenum and progressively diminishing concentrations throughout the remainder of the small intestine.

• The major form of gastrin in the circulation is "big gastrin" which has 34 amino acid residues, has sulfated and nonsulfated forms, a longer half life, and longer mode of onset of action. The longer biological half life of big gastrin may explain the relative preponderance of big gastrin in the circulation when compared with its proportionately smaller content in gastrinomas.

The various roles of gastrin are as follows: Stimulation of acid secretion and to a lesser extent pepsin secretion, stimulation of bile flow, inhibition of water and electrolyte absorption in the small intestine, contraction of the gastroesophageal sphincter, relaxation of the sphincter of Oddi, relaxation of the ileocecal sphincter, increase gastric mucosal blood flow, increase incorporation of amino acids into proteins in the gastrointestinal tract, contraction of gastric smooth muscle and release of insulin.

Measurement of gastrin by radioimmunoassay measures larger molecular forms as well as heptadecapeptide gastrin, and shows normal and duodenal ulcer patients to have fasting concentrations between 20 and 150 picograms (pg) per ml. After a protein meal, gastrin increases by 50 to 300 percent during the first hour.

Fasting hypergastrinemia can be found in patients with pyloric obstruction, achlorhydria and hypochlorhydria, gastric atrophy, gastric carcinoma, pheochromocytoma, retained gastric antrum in the afferent loop after gastrojejunostomy, and following vagotomy. Furthermore, patients with ZES can have day-to-day variations in gastrin values that are at times diagnostic and at other times only suggestive.

Consequently, provocative tests have been described to distinguish patients with ZES from those with duodenal ulcers. One is the calcium challenge test: Calcium gluconate is infused over a three-hour period at a rate of 12 to 15 mg of calcium per kg of body weight per hour. In patients with ZES there is a 2- to 3-fold increase in gastrin during the third hour accompanied by an increase in gastric acid secretion to rates similar to those observed with maximal histamine stimulation. Too few patients have been studied to establish strict criteria for ZES, but an absolute increase of greater than 500 pg per ml in serum gastrin is highly suggestive of ZES.

A second and more recently described provocative test for identifying patients with gastrinomas is that of secretin infusion. Secretin in man decreases gastric acid secretion probably by inhibition of both gastrin-mediated gastric secretion and inhibition of gastric release. In normals and patients with duodenal ulcer, secretin (3 units per kg of body weight per hour) lowers serum gastrin, whereas in patients with ZES there is a paradoxical increase in serum gastrin accompanied by acid hypersecretion.

Thus, a profile of serum gastrin concentration, which consists of the following may be described for patients with ZES: (1) elevated fasting serum gastrin concentrations in a patient who usually demonstrates gastric acid hypersecretion (values greater than 1,000 pg per ml are virtually diagnostic, and 200 to 1,000 pg per ml are suggestive), (2) exaggerated gastrin release in response to calcium infusion and (3) paradoxical increase in serum gastrin concentration following intravenous secretin infusion.

Therapy

As a general rule patients with ZES respond poorly to medical therapy. However, there have been no controlled clinical trials. One patient has been successfully treated with gastric irradiation with 2,200 roentgens. Streptozotocin has not proved effective.

The major mode of therapy, therefore, is surgical. In their review of 260 cases of ZES, Ellison and Wilson reported that 60 percent of ZES tumors were malignant and 44 percent were metastatic, with one half of these involving the liver. Only 30 percent of the tumors were identifiable benign adenomata. There was a 10 percent incidence of microadenomata alone. However, in another 9 percent of patients with either benign or malignant tumors microadenomatosis was present.

Of duodenal wall tumors, approximately 50 percent were benign solitary lesions and, therefore, the chance of a duodenal gastrinoma being solitary is greater than for pancreatic gastrinoma.

A more recent survey of the influence of

gastrectomy on survival in malignant gastrinomas reviewed the course of 267 patients.[14] In patients who had total gastrectomy there was a 55 percent five-year survival versus 27 percent survival for patients with lesser gastric procedures. Deaths from progressive tumor growth occurred in 17 percent of patients at risk after total gastrectomy versus 30 percent of patients at risk after lesser gastric surgery.

For patients with liver metastases in whom total gastrectomy was done, there was a 42 percent five-year survival versus 7 percent five-year survival with lesser gastric surgical procedures. Regression of metastatic tumors was clearly documented in only four patients, presumptive regression occurred in seven other patients—in all but two of these eleven patients total gastrectomies were done. In all patients in whom lesser gastric surgical procedures were carried out, the major causes of increased mortality were recurrent peptic ulcer disease and, to a lesser extent, deaths related to progressive tumor growth.

At present, several recommendations regarding therapy of ZES should be followed. (1) If parathyroid adenoma are present, these should be resected before undertaking abdominal surgical operation because pronounced improvement in diarrhea, steatorrhea and ulcer symptoms may occur. (2) If, at surgical operation, an apparently isolated solitary tumor is found without spread to lymph nodes or liver, it should be resected while monitoring gastric acid secretion. If acid secretion falls greatly, no gastric surgical procedures should be done. (3) Total gastrectomy should be done for all other patients. (4) Under no circumstances should total pancreatectomy and subtotal gastrectomy be done. One can never be sure that tumor is limited to the pancreas. If it is not, total gastrectomy will be required later and total gastectomy and total pancreatectomy are virtually incompatible with life.

REFERENCES

1. Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 25: 374-380, Sep 58
2. Verner JV, Morrison AB: Endocrine pancreatic islet disease with diarrhea. Arch Intern Med 133:492-500, May 1974
3. Kahn CR, Levy AG, Gardner JD, et al: Pancreatic cholera —Beneficial effects of treatment with streptozotocin. N Engl J Med 292:941-945, May 1975
4. Said SL: Vasoactive intestinal polypeptide: elevated plasma and tissue levels in the watery diarrhea syndrome due to pancreatic and other tumors. Clin Res (in press)
5. Bloom SR, Polak JM, Pearse AGE: Vasoactive intestinal peptide and watery-diarrhoea syndrome. Lancet 2:14-16, Jul 1973
6. Tompkins RK, Kraft AR, Zollinger RM: Secretin-like choleresis produced by a diarrheogenic nonbeta islet cell tumor of the pancreas. Surgery 66:131-137, Jul 1969
7. Klaeveman HL, Conlon TP, Levy AG, et al: Effect of gastrointestinal hormones on adenylate cyclase activity in human jejunal mucosa. Gastroenterology 68:667-675, Apr 1975
8. Elias E: Pancreatic cholera due to production of gastric inhibitory polypeptide. Lancet 2:791-793, Oct 1972
9. Zollinger RM, Ellison EH: Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 142:709-728, Oct 1955
10. Isenberg JL, Walsh JH, Grossman ML: Zollinger-Ellison syndrome. Gastroenterology 65:140-165, Jul 1973
11. Ellison BH, Wilson SD: The Zollinger-Ellison syndrome—Reappraisal and re-evaluation of 260 registered cases. Ann Surg 160: 512-530, Sep 1964
12. Ballard HS, Frame B, Hartsock RJ: Familial mutiple endocrine adenoma peptic ulcer complex. Medicine (Balt) 43:481-516, Jul 1964
13. Polak JM, Stagg B, Pearse AGE: Two types of Zollinger-Ellison syndrome: immunofluorescent, cytochemical, and ultrastructural studies of the antral and pancreatic gastrin cells in different clinical states. Gut 13:501-512, ul 1972
14. Fox PS, Hofmann JW, Decosse JJ, et al: The influence of total gastrectomy on survival in malignant Zollinger-Ellison tumors. Ann Surg 180:558-565, Oct 1974

Important Advances in Clinical Medicine

Epitomes of Progress—General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General and Family Practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General and Family Practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Cardiovascular Stress Testing

CARDIOVASCULAR STRESS TESTING is rapidly becoming a useful diagnostic and screening modality. Properly carried out and interpreted, a monitored test employing either a treadmill or a bicycle ergometer can be expected to yield definitive diagnostic S-T, T wave changes with a fair degree of reliability in patients in whom angina pectoris is suspected.

In this setting, false negatives (in persons found or known to have angiographically proven significant coronary artery disease) may represent up to 26 percent of those tested.

False positives occur less commonly (9.5 percent) and occasionally lead to diagnosis of the Lickoff syndrome (myocardial oxygen utilization defect).

As a screening device, stress testing has value in uncovering both silent coronary artery disease and dangerous stress induced arrhythmias. Although it would be ideal to be able to screen, for example, all adults over 40 years old, this has obvious logistical limitations. However, selection should include at least those adults with identified cardiovascular risk factors and certainly any sedentary persons contemplating entering an organized or prescribed exercise program. For the latter, a safe "target heart rate" to which the individual should exercise, may be rationally and logically determined.

In several epidemiologic studies of men over 40 years old in which 85 to 90 percent submaximal testing was used, asymptomatic coronary artery disease was uncovered at a rate of 10 to 28 percent.

Those general and family physicians with competency in interpretation of electrocardiograms and in cardiopulmonary resuscitation, and particularly those who are familiar with earlier

forms of testing such as Masters 2-step, should investigate increasing the scope and reliability of data obtainable through careful and properly monitored cardiovascular stress testing.

SAM SMITH, MD

REFERENCES

Kattus AA, Jorgenson CR, Worden RE, et al: S-T segment depression with near-maximal exercise in detection of preclinical coronary heart disease. Circulation 44:585, Oct 1971

McConahag DR, McCallister BD, Smith RE, et al: Post exercise electrocardiography: Correlations with coronary arteriography and left ventricular hemodynias. Am Cardiology 28:1, Jul 1971

Mason RE, Likar I, Brown RO, et al: Multiple lead exercise electrocardiography—Experience in 107 normal subjects and 67 patients with angina pectoris and comparison with coronary cineangiography in 84 patients. Circulation 36:517, Oct 1967

Tuberculin Testing 1975

WITH THE PRESENT PRACTICE of prolonged treatment of asymptomatic persons based on a positive tuberculin test, it is important for all providers of care to understand the tuberculin reaction, and be acquainted with more recently recommended procedures for tuberculin testing.

The size of the tuberculin reaction is related to the dose of tuberculin, whether old tuberculin (OT) or purified protein derivative (PPD) is used. Tests, such as the Tine® or Mono-Vacc® (jet injection) —which uses OT—or the Heaf (or Sterneedle®) —which uses PPD—are screening tests using a highly concentrated tuberculin antigen. Infection by mycobacteria other than Mycobacterium tuberculosis may cause cross reactions. Cross reactions between mycobacteria are usually smaller when the mycobacteria antigen is not specific, but are otherwise indistinguishable for a specific reaction. Any reaction to a high dose of tuberculin antigen may well be a cross reaction to atypical mycobacteria and all positive screening tests must be followed by a standard Mantoux's reaction test using a PPD intermediate strength (5 tuberculin units) and the reaction quantitated.

When reading a tuberculin test, only the induration is significant. Though there are some exceptions to them, guidelines for interpretation have been established and are shown in Table 1. Although it is customary to interpret the test at 72 hours, the tuberculin reaction remains essentially unchanged between 48 and 96 hours, so that a four-day reading is quite acceptable. Most cross-reactions between infections with M. tuberculosis and atypical mycobacteria occur when the standard Mantoux reaction falls in the doubtful area. Purified protein derivative from atypical mycobacteria gives a stronger reaction than PPD from M. tuberculosis if the patient is or has been affected with atypical mycobacteria. Standard tuberculin (PPD-S) gives a stronger reaction than PPD from atypical mycobacteria in persons with tuberculosis infection. There are several broad spectrum antigens for atypical mycobacteria available. Two, PPD Battey (PPD-B) and PPD Gause (PPD-G) have been tested in clinical trials. At the present time, PPD-B is recommended for testing for atypical mycobacteria infection. Comparative (dual) testing with standard PPD (PPD-S) and PPD-B is indicated when the tuberculin reaction falls in the doubtful area. Simultaneous Mantoux tests are placed with PPD-B and PPD-S, one in each forearm. Suggested guidelines for dual testing are shown in Table 2.

TABLE 1.—*Guideline for Interpretation of Induration*

Induration	*Interpretation*
0-4 mm	Negative
5-9 mm	Doubtful/undetermined
Greater than 10 mm	Positive

TABLE 2.—*Suggested Guidelines for Interpretation of Dual Testing*

PPD-S	*PPD-B*	
>10 mm		Indicates tuberculosis infection regardless of size of PPD-B reaction
5-9 mm	Smaller	Tuberculosis infection
	Same size	Doubtful for tuberculosis
	Larger	Infection with atypical mycobacteria

PPD-S = standard purified protein derivative
PPD-B = Battey purified protein derivative

A booster effect of tuberculin testing has been noted in some tuberculin reactors (not in tuberculin-negative persons). This is more common in older than younger persons and has been shown to occur as early as a month after testing, and lasts a year or more. Early dual testing after a doubtful Mantoux test or a positive tuberculin screening test will identify persons whose reactivity is the result of atypical mycobacteria infection and may eliminate the need for prolonged treatment.

WILLIAM C. FOWKES, JR, MD

REFERENCES

Palmer CE, Edward LB: Identifying the tuberculous infected. JAMA 250:167-169, Jul 1968

Smith DT, Johnston WW: The problem of "boost" effect in tuberculin skin testing. Am Rev Resp Dis 106:118-119, Jul 1972

Estradiol 17-Beta as a Predictive Factor in Premature Labor

If the high perinatal mortality and morbidity in infants of low birth weight is to be reduced, a means of predicting and preventing premature labor must be developed. Clinical criteria have failed to predict premature labor until it is too far advanced to be of therapeutic value.

For this purpose, premature labor has been defined as a labor arising spontaneously without a clear cause three or more weeks before term. This definition, of course, excludes patients in whom premature labor is associated with uterine or congenital fetal abnormalities, multiple pregnancies, hydramnios or systemic diseases of the mother.

Plasma progesterone and estradiol 17β levels have been measured serially from the 20th week of pregnancy up to and during spontaneous labor. The most common method of measurement has been by radioimmunoassay using specific antisera. A significant fall in progesterone and rise in estradiol occurs during the five weeks preceding labor.

Studies indicate that two events are necessary to trigger the onset of labor whether premature or at term: first, a surge in estradiol concentration and second, in the presence of this concentration, a decrease in the inhibitory effect of progesterone on uterine muscle activity. In some instances, estradiol concentration rose dramatically three to ten days before the onset of premature labor. It is this rise which is of value not only in predicting premature labor, but also in its prevention by suppression of the premature estradiol surge.

Now it appears that the increased concentration of plasma estradiol is the most clinically reliable measurement for predicting premature labor rather than the decrease in progesterone or an increasing ratio between the two.

At present, the cause of the sudden increase in plasma estradiol levels and its effect on uterine activity before a premature labor is only speculative. Two theories are suggested: High concentrations of plasma estradiol may directly stimulate uterine contraction or, alternately, estradiol may incite the synthesis of prostaglandin which could promote the same contractility.

One of the handicaps in clinical use of the plasma estradiol concentration in predicting premature labor lies in the interpretation of test results. In a normal pregnancy, plasma concentration of estradiol doubles between the 20th and 36th week rising from 4.7 to 10.3 ng per ml, and then doubles again in the last few weeks of pregnancy reaching a maximum of 21.0 ng per ml at 40 weeks. The surest way to avoid misinterpretation is to depend on serial assays in suspected premature labor patients. Isolated determinations may be misleading unless all these factors are considered.

Wilfred Snodgrass, MD

REFERENCES

Tamby RRL, Anderson ABM, Turnbull AC, et al: Endocrine changes in premature labor. Br Med J 4:67-71, Oct 1974

Turnbull AC, Patten PT, Flint AP, et al: Significant fall in progesterone and rise in oestradiol levels in human peripheral plasma before onset of labor. Lancet 1:101-103, Jan 26, 1974

Medical Treatment of Cholelithiasis

Approximately 16 million Americans have gallstones, 85 percent of which are primarily composed of cholesterol. In the past, surgical operation has offered the only definitive therapy for cholelithiasis, but the efficacy of drug therapy in dissolution of some gallstones is becoming well documented.

A necessary precursor to the formation of cholesterol gallstones is saturated bile containing insufficient bile acid and lecithin in proportion to cholesterol. A number of carefully controlled studies in recent years has established that the administration of chenodeoxycholic acid decreases cholesterol saturation of bile and dissolves gallstones. This action is exerted by replenishing the bile acid pool and by decreasing hepatic cholesterol synthesis and secretion. In two major studies, for example, more than a 50 percent decrease in gallstone size occurred in approximately half of those patients receiving chenodeoxycholic acid and, in some instances, there was complete dissolution of gallstones. This therapy is most effective for radiolucent gallstones, and is only occasionally effective in dissolving radiopaque gallstones. Side effects have been minimal, and there has been no evidence of liver damage from this therapy. Transient elevations of serum glutamic oxalacetic transaminase have been noted in some patients, but there was a return to pretreatment levels during continued therapy.

Although chenodeoxycholic acid has not yet been released for general use by the Federal Drug Administration, its value in providing safe and effective treatment for asymptomatic radiolucent

gallstones is becoming well established and warrants increasing interest by physicians caring for patients with this common problem.

JOHN P. GEYMAN, MD

REFERENCES

Coyne MJ, Bonorria GG, Chung A, et al: Treatment of gallstones with chenodeoxycholic acid and phenobarbital. N Engl J Med 292:604-607, Mar 1975

Thistle JL, Hofmann AF: Efficacy and specificity of chenodeoxycholic acid therapy for dissolving gallstones. N Engl J Med 289: 655-659, Sep 1973

Danzinger RG, Hofmann AF, Schoenfield LJ, et al: Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 286:1-8, Jan 1972

Radioimmunoassay

RADIOIMMUNOASSAY (RIA) provides a method to measure directly many substances that could be measured only indirectly or by animal biopsy before its discovery. It has found its greatest application in endocrinology, providing accurate measurements of very small amounts of circulating hormones. The clinical applications are too numerous to mention in this epitome, but a look at the hypothalamus-pituitary-thyroid axis will serve as an example.

Tests by RIA are available for triiodothyronine (T_3) and thyroxine (T_4). T_3 and T_4 values may be influenced by primary function of the thyroid gland, or by changes in the pituitary gland or the hypothalamus. The thyroid stimulating hormone (TSH) is elaborated in the anterior pituitary gland and is influenced by a hormone produced in the hypothalamus, the TSH releasing hormone (TRH). In turn TSH is suppressed by increased levels of T_3 and T_4 in the circulation.

It follows that one would expect to find a low TSH when there is excessive activity of the thyroid gland due to primary disease, that is, Graves' disease or toxic nodule. If the thyroid gland is hypofunctional, such as in Hashamoto's disease, thyroiditis or ablation of the gland by surgery or radioactive iodine, the TSH would be increased.

If the thyroid is hypofunctional because of disease of the pituitary gland, the TSH would be low as well as the T_4 and T_3.

To test the integrity of the anterior pituitary, TSH releasing hormone (TRH) may be given and a TSH level determined. If the TSH responds to the TRH the integrity of the pituitary has been established. Similar applications may be made to assess the function of many of the endocrine glands.

The advantages of RIA are reproducibility, accuracy, specificity, sensitivity, applicability to very small specimens and relative economy of replication. The reproducible results on the same specimen compare more closely than most other methods of assay. This is a tribute to the degree of accuracy possible with this method. The specificity of antibody/antigen reactions makes it possible to carry out the assay in a system containing many and variable amounts of other closely related substances. It is extremely sensitive, having capabilities to determine the presence of some antigens in the order of one trillionth of a gram (picogram) (10^{-12}gm) per milliliter. Because of the minute quantities of serum needed it is especially useful in pediatrics.

JAMES E. ANHALT, SR, MD

REFERENCES

Odell WD, Daughaday WD (Eds): Principles of Competitive Protein-Binding Assays. Philadelphia, J. B. Lippincott Co., 1971

Kasanof D: When radioimmunoassay is the test of choice. Patient Care 14:86-98, Aug 1973

Clonidine—A New Antihypertensive

CLONIDINE (Catapres®, Boehringer Ingelheim), 2-(2,6- dichlorophenylamino)-2- imidazoline hydrochloride, is a hypotensive agent that acts via central adrenergic blocking. Its order of potency is similar to other sympatholytic agents such as methyldopa (Aldomet®). It causes decreased peripheral resistance and decreased cardiac output, and may cause bradycardia. Cardiac response to exercise, however, is unimpaired. The drug also causes decreased sodium and chloride excretion, and must be used with diuretics. Serious toxicity—such as hepatorenal, oto- or marrow toxicity has not been reported. Serious side effects —such as impotence or orthostatic hypotension— are rare. Depression has been reported and tricyclic antidepressants antagonize the effect of clonidine. Common side effects are drowsiness, constipation and dry mouth; these tend to be transient, even in the face of increased doses. Renal blood flow is preserved or increased, and peripheral renin and aldosterone levels may be decreased; therefore, this drug may be particularly useful for those with decreased renal function or with hyperreninism or hyperaldosteronism.

Abrupt withdrawal of the drug can lead to sympathetic crises within 48 hours, manifest by anxiety, palpitations, sweating, headache and hypertension, and requiring treatment with pro-

pranolol and phentolamine. This effect is avoided by tapering the drug over two to four days. Onset of action is within two to four hours and serum half-life is 20 hours. Twice-a-day dosage is recommended. Administration is begun at 0.1 mg twice daily and increased until control is achieved or limiting side effects occur, up to a maximum of 2.4 mg daily. Clonidine should not be administered to unreliable patients, and patients receiving it should carry an extra supply and Medic Alert® or some other identification tag.

A. Robert Tessler, MD

REFERENCES

Medical Letter, Vol 1, No 11, May 23, 1975

Hoobler S: Clonidine hydrochloride in the treatment of hypertension. Am J Cardiology 28:67-73, Jul 1971

Baer L, Brunner HR, Bard R, et al: Suppression of renin and aldosterone by clonidine. Ann Intern Med 74:830, 1971

Gorchein A: Withdrawal of antihypertensive therapy. Lancet 2:1576, Sep 1974

Talwin Myopathy

Talwin (Pentazocine®) is a widely used analgesic. It has gained popularity because it was considered to be less addictive than other potent analgesics.

By 1971 at least two articles had appeared in the dermatology literature describing local reactions to Pentazocine injections. More recently, a much more profound and disabling reaction in the muscles termed "fibrous myopathy" was reported from several sources.

Two young men in their 30's were recently admitted, at the same time, to the chronic pain unit at Rancho Los Amigos Hospital. Both were suffering from fibrous myopathy of the deltoid area bilaterally, and this called the author's attention to this entity. Both young men had (A-B) abduction deformities and complained bitterly of their inability to cross the arm in front of them to carry out such functions as washing the opposite axillary fossa. One of the young men reported that his mother had undergone a surgical excision of both deltoid muscles to relieve this deformity which had followed use of Pentazocine over a period of time.

Steiner and co-workers reported a case with generalized abduction deformity of both upper extremities and lower extremities in a 42-year-old man who had persistent myalgia and progressive muscle stiffness. In this man the disability and rigidity progressed even though the injections had been terminated six months before he came under their care.

There are no specific enzyme or laboratory findings in this condition. The skin overlying the muscles may be atrophied and scarred to the fibrous degenerative muscles. Findings on electromyograms may show a mixed pattern or an interference pattern while at full effort. There is no muscle activity at rest as would be the case in other types of myopathy.

Temporary improvement has resulted in our patients by stretching and manipulating the tight upper extremities under general anesthesia. A brief course of prednisone is given at the time to minimize, it is hoped, re-scarring. Whether or not this treatment will give lasting benefit is very much in doubt. Avoidence of prolonged use of injectable Pentazocine seems the only rational approach to prevent this tragic disabling disorder.

J. Blair Pace, MD

REFERENCES

Steiner JC, Windelman C, de Jesus PV, et al: Pentazocine-induced myopathy. Arch Neurol 28:408-409, Jun 1973

Oh SJ, Rollins JL, Lewis I, et al: Pentazocine-induced fibrous myopathy. JAMA 231:271-273, Jan 20, 1975

Computers in Family Practice

The role of computers in medicine generally, and in family practice specifically, has been gathering increased interest in recent years but has remained unclear. An experience base is now developing which can start to answer some of the initial questions concerning its value in medical practice and education.

A group of three family physicians in Damariscotta, Maine, recently reported their experience over three years with direct computer-patient interactions both in military and private practice. In developing their computer program, this group applied four essential criteria: (1) relatively low cost, (2) extensive programing with medically compatible language, (3) terminal constellations which permit direct nonthreatening patient interaction and (4) no technological expertise required by office personnel. A computerized medical record was developed and selected administrative functions and other aids to patient care were incorporated into the computer program where needed and economically feasible. The computer was thereby used for patient histories, patient education, physician education

(consultation), paramedic guide of triage and examination, office billing and aids to diagnosis. Computer services were leased from a commercial supplier remote from the office at a cost of $1,200 to $1,300 per month. Personnel savings, together with billings for patient histories, patient education and paramedic routines, are projected to cover these costs. To date, cost savings, physician satisfaction and patient acceptance have been adequately shown.

Although further experience is needed to more fully assess the real value of computers in various family practice settings, the state of the art is becoming more refined and there is promise that computer applications can be developed which will improve the quality, efficiency and effectiveness of patient care in family practice.

JOHN P. GEYMAN, MD

REFERENCE

Morrison CC, Bostwick GW, Belknap SL, et al: The computer in family practice. J Maine Med Assoc 64:226-230, Oct 1973

Analgesics and Asthma

A SYMPTOM TRIAD of sinusitis, nasal polyps and asthma in response to aspirin sensitivity was first recognized more than 50 years ago. Aspirin and other analgesics, including indomethacin and paracetamol, may likewise precipitate an asthma attack in aspirin-sensitive patients.

This author has observed one aspirin-allergic patient with asthma who had repeated problems because he failed to recognize aspirin or related analgesics in various multi-drug mixtures. Each time a severe attack would occur, we would find the medication he had taken and discover in the fine print there was acetylsalicylate of some kind. The patient eventually died of agranulocytosis as a result of getting aspirin in a mixture which was not clearly labelled.

The group at Scripps Clinic and Research Foundation in La Jolla observed an 8 percent incidence of allergy to aspirin in patients referred to them. Many of the patients in this 8 percent group did not have the classic triad of nasal polyps and sinusitis. In this sense these persons were aspirin-sensitive but unrecognized as such.

The group at Scripps suggest cautious aspirin challenge under close supervision. The British express some misgivings about aspirin challenge, reporting that this has been known to prove fatal.

Family physicians would be well advised to think of aspirin as a potential allergen in all asthmatic patients, not only those with the nasal polyp sinusitis triad. It is also pertinent to realize that related analgesics, even though they have a very different chemical makeup, may produce the same asthmatic reaction.

J. BLAIR PACE, MD

REFERENCES

Mathison DA, Stevenson DD, Tan EM, et al: Clinical profiles of bronchial asthma. JAMA 224:1134-1139, May 21, 1973
Editorial comment. Br Med J 3:419-420, 1973

Metaproterenol as a Bronchodilator

METAPROTERENOL used throughout Europe and in Australia for the past ten years under the name of orciprenaline is now available in this country under the trade name Alupent®. It would appear to represent a significant improvement over previously available bronchodilator adrenergic drugs.

The action of metaprotherenol resembles that of isoproterenol, which has been widely used in this country. There are two distinctive advantages with metaproterenol. One of these is a 2- to 3-hour longer effectiveness, and the second is the availability and usefulness of metaproterenol as an orally administered medication. Metaproterenol, like isoproterenol, is a beta adrenergic drug with a greater affinity for the beta 2 receptors. Because of this, it does not produce pronounced cardiovascular effects. The usual effect is a slight, but not clinically significant slowing of the heart rate, with a slight drop of the blood pressure.

In comparison studies using metaproterenol and isoproterenol given by inhalation effectiveness was quite comparable, with response to metaproterenol being somewhat slower than response to isoproterenol. After 30 days of use, metaproterenol retained effectiveness up to four hours whereas isoproterenol retained effectiveness only up to one hour. After 60 days of use as an inhalant, metaproterenol retained effectiveness up to three hours with isoproterenol primarily effective only in the first five minutes.

Compared with ephedrine given orally, metaproterenol given orally in 20 mg doses appears to have a four-hour span of effectiveness without development of resistance. Ephedrine tends to be effective no more than three days if used continuously, after which the epinephrine stores are exhausted in the lung tissues and the ephredine

becomes inactive. As a new drug in this country, we have the security of knowing that metaproterenol has stood the test of time in the rest of the world.

J. BLAIR PACE, MD

REFERENCES

Kerr A, Gebbie T: Comparison of orciprenaline, ephedrine, and methoxyphenamine as oral bronchodilators. N Engl J Med 492:320-322, May 1973

Hurst A: Metaproterenol, a potent and safe bronchodilator. Ann Allergy 31:460-466, Oct 1973

Effective Thyroxine Ratio (ETR)

THE MOST ACCURATE measurement of thyroid function can be obtained by measuring the amount of free, unbound thyroxine (T_4), but an inexpensive assay has not been perfected for routine use. There is a precise correlation between serum T_4 concentration and thyroid status, providing the concentration of serum thyroxine-binding globulin (TBG) is normal.

Changes in the concentration of serum TBG are often associated with parallel changes in serum T_4 concentration even though the thyroid function is normal. Therefore a euthyroid woman in whom there is an increased concentration of TBG due to pregnancy or estogen ingestion often shows a T_4 concentration above normal. The effective-thyroxine ratio (ETR) reflects serum T_4 levels and automatically compensates to a large extent for variations in TBG.

If TBG concentration showed no variation in the normal population, then the value for the ETR would be determined entirely by the level of T_4. For this reason there is a very high linear correlation between ETR and T_4 when patients with TBG abnormalities are excluded.

Although estrogens and progestins are the most frequent causes of increased T_4 serum concentration, sulfamethoxazole, chloramidinone, clofibrate, perphenazine and residual radioactivity also cause an increase. Decreases in T_4 can be caused by at least 30 different drugs by either decreasing T_4 synthesis, by increasing T_4 destruction, by decreasing the amount of TBG or by displacing T_4 from binding sites.

Anything that increases TBG will increase the measurable T_4 or protein bound iodine, but will reduce the triiodothyronine (T_3) proportionately.

The ETR measures only that concentration of T_4 that determines thyroid function, and is expressed as a ratio with T_4 similarly determined in normal serum.

The ETR should not be confused with the FTI (free-thyroxine index). The FTI is also an accurate measurement of thyroid function and is calculated for each patient, $T_3 \times T_4 \times 100$. The ETR is a competitive protein-binding assay and correlates well with the FTI and could replace the more complicated FTI procedure in patients with known abnormalities of binding proteins and suspected thyroid disease.

Several studies now show that the ETR is the best single and practical test of thyroid function. The results, however, (normal range: 0.86 to 1.13) should be carefully interpreted: In hypothyroidism the decreased level may not correlate well with the degree of hypofunction. For instance, a 0.84 may represent a rather severe hypothyroidism with myxedema. The other area of misinterpretation is in patients who have received ^{131}I or antithyroid drugs and are euthyroid. These patients tend to have low ETR scores.

WILFRED SNODGRASS, MD

REFERENCES

Powers JS, Roach C, Berdon T, et al: The effective thyroxine ratio as a test of thyroid function. Obstet Gynecol 44:806-810, Dec 1974

Thorson SC, Mincey EK, McIntosh HW, et al: Evaluation of a new in-vitro blood test for determining thyroid status: the effective thyroxine ratio. Br Med J 2:67-71, Apr 8, 1972

Combination Therapy of Parkinson's Disease

BY COMBINING a decarboxylase inhibitor with L-dopa at a fixed ratio of one part inhibitor called carbidopa to ten parts of levodopa or L-dopa, three definite advantages have been achieved over the use of the single drug levodopa. First, the combination causes less nausea and vomiting. Second, the combination brings about therapeutic results more quickly. Third, additional improvement occurs in patients who have reached the maximum improvement or the maximum tolerance of the single drug.

Major central nervous system side effects—such as involuntary movements and mania and other psychiatric disturbances—occur as frequently with the combination as they do with the single drug.

The effective dosage range with the combination drug is very broad and varies from a low of 30 mg carbidopa, plus 300 mg levodopa, to a

high of 200 mg carbidopa and 2,000 mg levodopa. The average effective dose appears to be in the general neighborhood of 100 mg carbidopa combined with 1,000 mg of levodopa. At this level total dosage of levodopa is lower and tolerance better than with previous experience in which doses as high as 3, 5 and 8 grams per day of levodopa were administered. Many patients obtain a degree of control comparable to, or better than, previous control on levadopa alone by taking only 20 percent of their previous dosage of levodopa supplemented by carbidopa in the one to ten ratio. A one to ten fixed combination of carbidopa and levodopa is marketed by Merck, Sharp and Dohme under the name Sinemet.®

J. Blair Pace, MD

REFERENCES

Markham CH, Diamond SG, Treciokas LJ: Carbidopa in Parkinson disease and nausea and vomiting of levodopa. Arch Neurol 31:128-133, Aug 1974

Marsden CD, Parkes JD, Rees JE: Long term treatment of Parkinson's disease with an extracerebral dopa decarboxylase inhibitor, L-alpha-methylodopahydrazine and levodopa, *In* Caine DB: Advances in Neurology. New York City, Raven Press, 1973, chap 3, pp 79-96

ADVISORY PANEL TO THE SECTION ON GENERAL AND FAMILY PRACTICE

Benson McGann, MD, *Chairman*
CMA Scientific Board, Los Altos

Nicholas P. Krikes, MD
CMA Section on General and Family Practice, Chairman
San Bernardino

John Bridgeman, MD
CMA Section on General and Family Practice, Secretary
Mission Viejo

Sam W. Smith, MD
CMA Section on General and Family Practice, Assistant Secretary
Lemon Grove

Frank Gaspar, MD
Loma Linda University

William Fowkes, MD
Stanford University

John D. Crivaro, MD
CMA Scientific Board
Long Beach

J. Blair Pace, MD
CMA Scientific Board
Orange

Wilfred J. Snodgrass, MD
CMA Scientific Board
Santa Monica

Holger Rasmussen, MD
Fremont

John Geyman, MD
University of California, Davis

Raymond C. Anderson, MD
University of California, Irvine
California College of Medicine

L. Robert Marvin, MD
University of California, Los Angeles

Richard Barnett, MD
University of California, San Francisco

Simon C. Brumbaugh, JR, MD
CMA Scientific Board
University of California, San Diego

EDITORIALS

A Job Action by Physicians

CALIFORNIA PHYSICIANS are aware, but others may not be, that the California Medical Association has sponsored bills in the California legislature every year for at least five years seeking relief from or some solution to the malpractice problem. In one sense these bills may even then have been after the fact in that it may have been no longer possible to prevent an inevitable crisis. But in another very real sense they were ahead of their time in that none of those concerned—not the average physician, nor the legislature nor the public—was ready to give this problem their full attention or support. Be this as it may, the record will show that while this early, forward looking and persistent effort of the CMA produced some results, these were obviously less than what was desirable or needed. Inevitably the issue came to a head when the laws as written, court interpretations of the law and court awards or judgments against physicians and hospitals finally overwhelmed the presently existing system of professional liability insurance.

An intolerable situation developed when several thousand physicians in northern California were suddenly informed that their professional liability insurance premiums would be tripled or quadrupled and that for some highly technical and high-risk specialties the rates would be between $15,000 and $25,000 a year.

The reaction among physicians in high-risk specialties, particularly anesthesiology, was immediate. This additional cost was more than they felt could or should be passed on to their patients. A job action, a widespread withholding of professional services, developed almost spontaneously. The power of this approach proved to be almost frightening. Elsewhere in this issue the impact of this withholding of physicians' services upon a major urban community hospital is described—with sympathy for the physicians, but also with a firsthand account of what this can mean to a community hospital, the hospital personnel and the patients the hospital normally serves. The implications are truly far-reaching. It seems very evident that job actions by physicians such as this can effectively destroy the fiscal integrity of private nonprofit community hospitals, and do this quite quickly and quite unintentionally, with serious immediate and long-range implications for the viability of private sector in patient care.

Again, as California physicians know but others may not, the California Medical Association has responded by launching a massive effort for legislative reform and public understanding of this problem which strikes at the very heart of patient care in this nation. One senses that there is now a growing understanding of the problem, and that if reason prevails, and all groups and factions work together rather than competitively or at odds, a solution can be found that all can live with. If this can be accomplished somehow, medical care will be strengthened not only in California but in the nation.

—MSMW

Clinical Care of Burned Patients

THE CARE of burned patients is still one of the most difficult and complex challenges in medicine. Approximately 20 years ago, the late Carl Moyer rather shocked the American Surgical Association when he reported, using source data from papers written approximately 50 years apart, that the mortality rate of burned patients had not changed since the end of the 19th century. Despite massive advances in fluid resuscitation which had occurred in the early part of this century, and despite the increased survival of burned patients through the period of "burn shock," overall survival had not increased. A paper on "Advances in the Clinical Care of Burned Patients" by Curreri and Marvin in the current issue, clearly shows why. The complexity of the burn problem literally assures that no one advance will affect long-term

survival unless it is accompanied by equal advances in a number of other areas.

In the last 20 years, advances have occurred in six major areas of the burn problem, and it has taken all these advances to materially affect overall survival. Not only has it been necessary to improve methods for fluid resuscitation, but it has been necessary to develop topical antibacterial agents to prevent burn wound sepsis and special techniques to detect and define burn wound infection. Large quantities of biological dressings (skin heterograft and homograft) can now be obtained. Operative techniques for the removal of eschar and placement of early autograft have been improved. The massive nutritional requirements of a burned patient have finally been appreciated, and methods of preventing the excessive scar formation which once inevitably followed burn injury have been devised. Curreri and Marvin have described the state of the art as it exists today.

None of these improvements represents a single step made by a single person or team. Each is the result of the kind of hard, slogging work which characterizes the care of a burned patient. Literally hundreds of investigators have added their bit to the painful but inexorable progress. It is now predictable that burn care will become increasingly effective in the years to come. This is not to say that there may not be a seventh or eighth or even tenth area which might be defined and in which progress might be made. For instance, the well known fact that a burn wound increases in depth in the few days following injury has not yet excited the curiosity of more than a handful of investigators. If means can be developed by which this early progression of the burn wound depth can be prevented, a further solid step would be taken. Another fundamental area of potential improvement is in reenforcing or even selective suppression of the immune mechanisms.

Although they have not included it in their accounting of six major advances, the authors show the other major change which has occurred in the last ten years. It is now generally agreed that a burn patient needs specialized care, under specialized circumstances, under a team of therapists. Recently, this was recognized in California law. The authors of this paper, a surgeon and a nurse, represent the team approach. It is in burn units, in the hands of teams of therapists, that the many individual advances are, at last, reaping the rewards of salvage of human life and human function that we have long expected of them. One regrets only that many of the original pioneers have not lived to see the ripest fruits of their labors.

THOMAS K. HUNT, MD
Professor, Department of Surgery
University of California, San Francisco

Croup and Epiglottitis

THE SPECIALTY CONFERENCE elsewhere in this issue conducted by the Departments of Pediatrics and Radiology at the University of California, San Diego, provides the reader with a refreshing opportunity for direct analysis of contemporary diagnosis and management of one of the most provocative issues of emergent pediatric care, namely, acute infectious obstruction of the upper respiratory tract.

Fortunately, acute bacterial epiglottitis is rare, but the spectre of this fulminant infection should stalk the mind of every diagnostician who confronts a child with stridor. For every 100 children with acute obstructive viral laryngotracheitis (croup), one child may emerge with epiglottitis. Incidentally, the diagnosis of acute laryngotracheitis does not uniformly imply obstruction of the upper airway, despite the presence of hoarseness and cough.

A youngster with abrupt stridor due to epiglottitis is rarely hoarse. However, since these children are so often unable to utter any sound, this traditional point of differential diagnosis may be meaningless. The sudden onset of nocturnal, stridulous breathing in an afebrile child with barking cough and hoarseness, easily ascertained over the telephone, demands an examination. If not carried out immediately, the examination should be done promptly within one to two hours if the therapeutic sequence of repose in a steaming bathroom and administration of ample liquids and syrup of ipecac does not resolve the problem. If the illness quickly subsides, one is dealing most likely with acute spasmodic croup. Telephonic verification of barking cough and hoarseness, without obstruction, does not require examination unless the laryngotracheitis progresses.

When examining a child with typical laryngotracheitis, the patient should be evaluated in the sitting position with the thorax thrust forward,

head extended, mouth widely open, a tongue-blade gently applied to the anterior tongue. Strong light should be used. A normal epiglottis will usually appear. If obstruction is particularly severe, a lateral x-ray film of the neck should be made to confirm the anatomical process and, as the group from UC San Diego point out, a physician should be present. If one suspects the rare case of epiglottitis, the lateral x-ray film of the neck should be obtained first, with the team of clinician, otolaryngologist and anesthesiologist in attendance; if the roentgenogram indicates epiglottitis, the same team should transport the patient to the operating room, continue the diagnosis by direct, controlled visualization, then carry out a tracheostomy, obtain pharyngeal and blood cultures and initiate parenteral antimicrobial therapy.

Although nasotracheal intubation has been used successfully by several centers throughout the country for the management of acute epiglottitis, the majority of clinicians and surgeons will wish to employ swift, facile tracheostomy. There is no place for anticipatory nonsurgical observation, inhalation of racemic epinephrine or use of systemic corticosteroids when a *conclusive* diagnosis of epiglottitis has been made. A perusal of the nuances located between the lines of the recent literature and personal observation suggest that lateral x-ray films of the neck do not always provide a conclusive diagnosis of epiglottitis.

Tracheostomy is seldom required for a child with acute viral laryngotracheitis. Careful, sequential, clinical observation in the setting of modern intensive care units, supplemented by the judicious use of arterial blood gas analyses, will determine the candidates for tracheostomy. Nasotracheal intubation is inappropriate for this illness because of the damage incurred by inflamed, edematous mucosa. While mist tents represent a likely therapeutic myth for pneumonitis and bronchiolitis, in our experience topical aerosolization of distilled water can diminish dramatically the subglottic pathophysiology of laryngotracheitis. The humidification of concomitantly administered oxygen is adjunctive and reasonable since ventilation-perfusion dysequilibrium, highlighted by hypoxemia and eucapnia, occurs with laryngotracheitis. Indeed, these respirovirus infections probably represent diffuse nasopharyngolaryngotracheobronchopneumonitis. Intensive parenteral fluids may achieve the same therapeutic result, if restorative oxygen could be shown to be superfluous. Recent controlled studies of the use of intermittent racemic epinephrine in the management of acute laryngotracheitis suggest that the beneficial effect is short-lived, the natural history of the disease is unaltered, and the most compelling benefit is the delivery of aerosol to the subglottic region. Corticosteroid therapy of laryngotracheitis remains an enigma. One would anticipate that antiphlogistic therapy should be beneficial, but, in fact, only one of numerous controlled studies indicates that corticosteroids hasten the clinical recovery of children with acute viral tracheobronchitis.

Drama, controversy, sustained inquiry and new knowledge insure the continued viability of a biomedical topic; the vicissitudes of the diagnosis and treatment of acute viral laryngotracheitis and bacterial epiglottitis offer such a compelling agenda.

JOSEPH W. ST. GEME, JR, MD
Professor and Chairman
Department of Pediatrics
Harbor General Hospital, Torrance
University of California, Los Angeles
School of Medicine

The First Decade of Federal Medicine

IT IS NOW almost exactly a decade since the federal government began to become seriously involved in the day-to-day delivery of medical care. Before 1965 there had been substantial and very productive federal support of medical research but direct intervention in medical education and patient care had been mostly talk with very little action. The national election of 1964 was interpreted by those elected to be a mandate for massive government action in the field of health care. During 1965 the Congress passed the first of what was to become a series of laws and programs attempting to deal with the widely proclaimed "health care crisis." While there were many who doubted the crisis was real in 1965 it is safe to say that whatever crisis there was has become a real mess in 1975, the result of attempts to administer poorly conceived laws and of various court actions which have also profoundly affected patient care.

The clock cannot be turned back. That alternative is not open to us. Rather the clock ticks on. The only value of looking back is to see what can

be learned that may be of use now or in the future. As one reviews the past decade, with its wave after wave of new health legislation, one is impressed with how much the costs have risen while there has been comparatively little improvement in health or health care directly attributable to the government programs, and with the fact that most of the federal programs simply have not worked. Rather federal programs have imposed a variety of regulations, requirements and restrictions which have had the effect of shackling the delivery system and increasing the cost of doing the same thing and very little more, when the goal was to bring many more services to many more people. Medicare might be viewed as an exception to this. Medicare seems to be running fairly smoothly and serving its purpose of helping the elderly with their substantially greater health care needs, although the program does not adequately meet the costs of the care rendered to its beneficiaries, particularly when they are in hospital, and forces the subsidization of Medicare patients by other hospital patients, providers or other sources.

One cannot help wondering whether the congressmen and senators who passed the bills and the presidents who signed them into law really ever understood all the implications and ramifications of the health legislation of the past decade. Of course they did not—nor could they have all been expected to. And if they themselves did not understand it, to whom did they look for advice and guidance? The record of the past decade suggests that they have depended heavily on their own staffs and the power seeking bureaucracies in the Department of Health, Education, and Welfare. The input from the real world of medical practice and patient care, from those who must live with the legislation and try to make it work, has not been particularly welcome and has been relatively ineffectual in the places where these laws and programs have been decided upon and designed. Again, Medicare itself (Title XVIII of the Society Security Act) might be an exception. This was discussed over a period of years and the input from the real world of practice was loud and clear. Perhaps this has something to do with why Medicare seems on the whole to have worked better than most of the other programs.

If it is true that much of the difficulty with the health legislation of the past decade has been that it has been conceived, enacted and administered without "including in" the real world of health care and those who must make it work if it is going to work, then who is to blame and what can be done to improve things in the future? As is usual in such situations there seems to be enough blame to go around for everyone, whether in the public or private sector, and part of the trouble may be a weakness in the democratic system itself, both in and out of government. In any case it is entirely clear that the health legislation of the past decade has been something less than a cooperative effort between government and those in the private sector who must make the laws work. In fact it has been quite the opposite. Government has sought to impose its will upon the private sector (which it should actually be serving in our system) and the private sector has so far failed to come up with workable solutions to problems identified by government and others as unmet health care needs of the people. And it must be admitted that the democratic system, under which both sectors operate, simply does not adapt easily to long-range planning, to the problems of human interdependence whether in health care or anything else or to the pursuit of any single course of action over any considerable length of time.

What is to be done? First there must be a counterforce to oppose the evident determination of the federal government to impose its will unilaterally upon the private sector in health care. This has just started. The private sector has begun to seek relief from the courts and reluctantly resorted to limited job actions to make their points. But these activities, necessary though they may be, will never clear up the mess which is only getting messier. Rather they will add to it. A second step is needed. The private sector should begin to recognize the health care problems for what they are and develop its own goals and objectives for what should be done in health care, based on firsthand experience with the problems. This will require a coordinated effort in the private sector, perhaps through some kind of coalition of agencies and associations. This second step should lead to a third. Since neither the private sector nor government can do it alone, a new and truly cooperative relationship should develop between the two. In this relationship, as in all others, it should be the role of government to be the servant and not the master of the people. As a practical matter, this can only occur when the people, in this case those responsible for the delivery of health care, have recognized the un-

solved problems for what they are, and devised workable solutions or approaches to solutions for them. If such a genuine partnership between government and the people, including the health professions, were ever to come about, it might also then be possible to address the as yet unsolved problem of long-range planning within a democratic system, and the steady pursuit of a single course of action over a considerable length of time—an accomplishment which is actually essential for the survival of any democratic society in today's interdependent world.

The second decade of federal medicine, begun in 1975, is pregnant with opportunities to make our system work. It also carries the potential, perhaps even the likelihood, of compounding the mess which has been created. The first decade has been pretty well botched. Let us hope there will be a chance for us all to get together and do a better job of it in this next decade.

—MSMW

Pancreatic Cholera

PANCREATIC CHOLERA is a relatively rare clinical syndrome characterized by a non-beta islet cell pancreatic neoplasm, profuse watery diarrhea, hypokalemia and metabolic acidosis.[1-3] Although in most of the published case reports patients with this syndrome have had an intraabdominal neoplasm or pancreatic non-beta islet cell hyperplasia,[4] recently we and others[5,6] have seen patients who have all of the clinical manifestations of pancreatic cholera but in whom no intraabdominal pathology is found at laparotomy or postmortem examination or both. Patients in whom no pathology is found constitute a particularly frustrating problem for clinicians, since such a patient's unremitting, fulminant diarrhea serves as a constant stimulus for physicians to carry out more extensive (and usually more invasive), hazardous diagnostic procedures to "find the tumor." Evidence that pancreatic cholera may be associated with extraabdominal neoplasms is found in the report by Said and Faloona[5] of five patients in each of whom there was pancreatic cholera syndrome and bronchogenic neoplasm. This observation has obvious important implications for the diagnostic evaluation of patients with pancreatic cholera and one hopes that adequate documentation of this association will be forthcoming in future publications.

From the clinical standpoint the pathogenesis of pancreatic cholera originates with a pronounced net secretion of isotonic fluid along the entire length of the small intestine. It has yet to be established whether this net secretion results from decreased absorption, increased secretion or a combination of the two processes. Whatever the mechanism, the result is that the colon is presented with excessive volumes (as high as 20 liters per 24 hours) of isotonic fluid having sodium, potassium and chloride concentrations similar to those in plasma. The mechanism through which the colon reabsorbs sodium and chloride can be conceptualized as involving two "exchange processes": sodium-for-potassium and chloride-for-bicarbonate.[7] Thus, colonic absorption of sodium and chloride is accompanied by an increase in the intraluminal concentration of potassium and bicarbonate. In the pancreatic cholera syndrome colonic absorption of sodium and chloride is maximal and there is an associated maximal colonic "secretion" of potassium and bicarbonate. The fecal loss of the latter two ions is primarily responsible for the hypokalemia and metabolic acidosis seen in this disorder. The hypokalemic acidosis can be significantly ameliorated in some patients by continuously aspirating ileal fluid using a tube with its tip positioned just above the ileocecal valve. This procedure, however, significantly increases the patient's total body loss of sodium chloride and parenteral administration of these ions must be increased correspondingly.

The large fecal losses of water and electrolytes in this syndrome necessitate careful monitoring of the patient's state of salt and water balance and vigorous parenteral replacement therapy. When patients are first seen they are usually dehydrated and occasionally hypotensive. As they are given intravenous fluid their stool output increases and the greater the amount of fluid administered parenterally the greater the fecal losses. The difficult clinical decision to be made under these circumstances is what should be the patient's daily intake of salt and water. For example, in a patient with fecal losses of 12 to 16 liters daily the physician is continuously trying to determine to what extent the patient's fecal output is occurring solely in response to parenteral fluid administration and to what extent the fecal volumes represent the patient's "basal diarrheal state." Usually

one attempts to provide sufficient fluid and electrolytes to maintain intravascular volume and urine output without overloading the patient's cardiovascular system.

Hypercalcemia is frequently present in patients with pancreatic cholera and on several occasions we have observed pronounced increases in serum calcium (to near lethal concentrations) following rapid intravenous administration of large volumes of saline. Serum calcium should be determined frequently in patients with pancreatic cholera particularly during the initial period of rehydration and any time the rate of parenteral fluid administration is increased.

Although surgical operation has been the primary mode of therapy for pancreatic cholera,[8,9] corticosteroids have reduced the diarrhea in certain patients.[9] Recently two patients have been treated successfully with streptozotocin administered via a hepatic artery catheter[10] and we know of four additional patients who have had excellent clinical responses to streptozotocin administered intravenously. Although streptozotocin appears to offer great promise for patients with pancreatic cholera and metastatic tumor, surgical operation still remains the initial therapy for this disorder.

At present, the leading etiologic candidate for the pancreatic cholera syndrome is vasoactive intestinal peptide (VIP)—an octacosapeptide originally isolated from hog small intestinal mucosa[11,12] and subsequently found to produce functional alterations in a number of tissues *in vivo* and *in vitro*.[11,13] The biologic actions of VIP make it a reasonable candidate for the etiologic agent in the pancreatic cholera syndrome. Like cholera toxin and prostaglandins, each of which can produce clinical syndromes characterized by watery diarrhea, VIP stimulates adenylate cyclase,[14,15] increases cellular cyclic adenosine monophosphate (AMP) and produces net secretion of water and electrolytes[14] in small intestinal mucosa *in vitro*. Elevated concentrations of VIP by radioimmunoassay have been reported in plasma and tumor tissue from patients with pancreatic cholera.[5,6] Said and Faloona[5] also found increased plasma VIP in patients with pancreatic cholera but without a demonstrable neoplasm; however, Bloom[6] found plasma VIP to be normal in each of eight such patients.

There are several apparent discrepancies which have to be resolved before the precise role played by VIP in the pancreatic cholera syndrome can be considered established. There are occasional asymptomatic normal subjects who have plasma VIP concentrations equal to or greater than those seen in pancreatic cholera.[5] On the other hand, some patients with pancreatic cholera and a nonbeta islet cell pancreatic neoplasm have plasma VIP concentrations which are not elevated.[10] The concentrations of VIP required to stimulate adenylate cyclase, cellular cyclic AMP and intestinal secretion *in vitro* are approximately 100 times greater than the highest plasma concentration of VIP in patients with pancreatic cholera.[14,15] In two patients with pancreatic cholera[10] intestinal adenylate cyclase activity was normal rather than elevated as one would expect from *in vitro* studies. Finally, in animals VIP is a potent vasodilator and hypotensive agent[11,13]; conversely, in patients with pancreatic cholera hypotension is not common and when present is usually attributable to dehydration and hypovolemia secondary to the diarrhea.

JERRY D. GARDNER, MD
Chief, Section on Gastroenterology
Digestive Diseases Branch
National Institute of Arthritis, Metabolism, and Digestive Diseases
Bethesda, Maryland

REFERENCES

1. Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 25: 374, 1958

2. Matsumoto KK, Peter JB, Schultze RG, et al: Watery diarrhea and hypokalemia associated with pancreatic islet cell adenoma. Gastroenterology 50:231, 1966

3. Walsh JH, Sleisenger MH: Syndromes caused by functioning islet cell tumors, *In* Sleisenger MH, Fordtran JS (Eds): Gastrointestinal Disease. Philadelphia, W. B. Saunders, 1973, p 365

4. Verner JV, Morrison AB: Endocrine pancreatic islet disease with diarrhea—Report of a case due to diffuse hyperplasia of nonbeta islet tissue with a review of 54 additional cases. Arch Intern Med 133:492-499, 1974

5. Said SI, Faloona GR: Elevated plasma and tissue levels of vasoactive intestinal polypeptide in the watery-diarrhea syndrome due to pancreatic bronchogenic and other tumors. N Engl J Med 293:155-160, Jul 24, 1975

6. Bloom SR, Polak JM: The role of VIP in pancreatic cholera, *In* Thompson JC (Ed): Gastrointestinal Hormones. Austin, Univ. Texas Press, 1975, p 635

7. Fordtran JS: Diarrhea, *In* Sleisenger MH, Fordtran JS (Eds): Gastrointestinal Disease, Philadelphia, W. B. Saunders, 1973, p 291

8. Kraft AR, Tompkins RK, Zollinger RM: Recognition and management of the diarrheal syndrome caused by nonbeta islet cell tumors of the pancreas. Am J Surg 119:163-170, Feb 1970

9. Schein PS, DeLellis RA, Kahn CR, et al: Islet cell tumors: Current concepts and management. Ann Intern Med 79:239, 1973

10. Kahn CR, Levy AG, Gardner JD, et al: Pancreatic cholera: Beneficial effects of treatment with streptozotocin. N Engl J Med 292:941-945, May 1, 1975

11. Said SI, Mutt V: Polypeptide with broad biological activity: Isolation from small intestine. Science 169:1217-1218, Sep 18, 1970

12. Said SI, Mutt V: Isolation from porcine intestinal wall of a vasoactive octacosapeptide related to secretin and to glucagon. Eur J Biochem 28:199-204, 13 Jul 1972

13. Said SI: Vasoactive intestinal polypeptide (VIP): Current status, *In* Thompson JC (Ed): Gastrointestinal Hormones. Austin, Univ. Texas Press, 1975, p 591

14. Schwartz CJ, Kimberg DV, Sheerin HE, et al: Vasoactive intestinal peptide stimulation of adenylate cyclase and active electrolyte secretion in intestinal mucosa. J Clin Invest 54:536-544, Sep 1974

15. Klaeveman HL, Conlon TP, Levy AG, et al: Effects of gastrointestinal hormones on adenylate cyclase activity in human jejunal mucosa. Gastroenterology 68:667, 1975

CASE REPORTS

Refer to: Carmalt JE, Theis J, Goldstein E: Spinal cysticercosis. West J Med 123:311-313, Oct 1975

Spinal Cysticercosis

JANICE E. CARMALT, MD
JEROLD THEIS, DVM
ELLIOT GOLDSTEIN, MD
Davis, California

INFECTION OF HUMANS with the larval form of the tapeworm, Taenia solium, is common in some parts of the world including Mexico. Sites of infection commonly include the eyes, subcutaneous tissues, muscles, and the brain; less commonly involved are the heart, liver, lungs, abdominal cavity and quite rarely, the spinal cord.[1] In our patient, features consistent with either a spinal cord tumor or tuberculous meningitis were seen. In fact, however, cysticercosis of the spinal cord was present.

Report of a Case

A 24-year-old Mexican farm laborer was transferred to the Neurosurgical Service of the University of California, Davis-Sacramento Medical Center in July 1974 after findings on a myelogram done at an outside hospital showed multiple filling defects. While in Mexico in 1961 the patient had had an episode of "complete paralysis" which resolved after six months. He was told he had recovered from poliomyelitis. In 1969 he was admitted to a hospital in California with fever and meningismus. A specimen of cerebrospinal fluid (CSF) showed the following on testing: leukocytes 18,000 per cu mm with 82 percent polymorphonuclear leukocytes; protein 196 mg per 100 ml; glucose 6 mg per 100 ml. Because tuberculous meningitis was considered likely, antituberculous therapy was instituted; however, cultures of the lumbar CSF for acid-fast bacilli, fungi and bacteria were sterile. The patient evidently recovered and was well until the present episode occurred.

In early 1974, the patient noted progressive weakness and muscle fatigue of both legs with cramping in the left leg, and mild, evanescent headaches. In April 1974, he experienced eight days of fever and stiff neck; in May 1974, severe headaches, nausea, vomiting and low back pain which radiated to both legs developed. The medical history was otherwise unremarkable. The only familial disease was epilepsy in a brother living in Mexico.

On physical examination, mild paraspinous tenderness in the region of the fourth to fifth lumbar vertebrae was noted, with no sciatic notch tenderness. Straight leg raising to 30° bilaterally produced back pain with lower extremity radiation. Cranial nerves, deep tendon reflexes, gait and sensory examination findings were normal. The hemoglobin was 13.4 grams per 100 ml, the hematocrit was 39.7 percent, the leukocyte count was 8,700 per cu mm with 60 percent polymorphonuclear leukocytes, 1 percent bands, 21 percent lymphocytes, 5 percent eosinophiles, 4 percent basophiles and 8 percent monocytes. Liver function tests gave findings within normal limits except for lactic dehydrogenase of 250 mu per ml (normal 100 to 225 mu per ml) and total protein 8.2 grams per 100 ml (normal 6 to 8 grams per 100 ml). Results of urinalysis, and prothrombin time and partial thromboplastin time were normal. By serum immunoelectrophoresis, the immunoglobulin M (IgM) was 170 mg per 100 ml (normal 50 to 110 mg per 100 ml) with normal concentrations of immunoglobulin G (IgG) and immunoglobulin A (IgA). Roentgenograms of the chest, lumbosacral spine, skull and

From the Section of Infectious and Immunologic Diseases, Department of Internal Medicine (Drs. Carmalt and Goldstein); and Department of Medical Microbiology (Dr. Theis); University of California, Davis, School of Medicine.

Submitted February 3, 1975.

Reprint requests to: J. E. Carmalt, MD, Department of Internal Medicine, Section of Infectious and Immunologic Diseases, University of California, Davis, School of Medicine, Davis, CA 95616.

right hip were interpreted as normal; no calcifications were seen.

The day after admission, multiple filling defects were seen on myelography in the lumbar and thoracic regions and were radiologically consistent in appearance with neurofibromas (Figure 1). Cerebrospinal fluid obtained at myelography contained 154 mg of protein per 100 ml; 10 mg of glucose per 100 ml; 196 leukocytes per cu mm with 5 percent polymorphonuclear and 95 percent mononuclear cells. India ink stain, acid-fast stain, Gram stain, acid-fast culture, bacterial and fungal cultures gave negative results. By cytologic examination, sheets of cells were noted which were thought to be ependymal in origin. A Gallium-67 scan showed increased uptake in the area of the fourth to fifth lumbar vertebrae. Eleven days after admission, papilledema was noted but the patient was alert, oriented and otherwise unchanged neurologically. There were no abnormalities found on electroencephalography, brain scan and orbital venography. Thirteen days after admission, the lumbar cerebrospinal fluid was under a pressure of 90 mm of mercury; protein, 216 mg per 100 ml; glucose, 3 mg per 100 ml; leukocytes, 27 per cu mm with 18 percent polymorphonuclear and 82 percent mononuclear cells. Again search for microorganisms was unrewarding.

Fourteen days after admission, somnolence, meningismus and a temperature of 39°C (103°F) developed. Antituberculous therapy was begun, but the patient failed to improve. Ventriculography and cerebral arteriography documented the presence of communicating hydrocephalus, and raised the possibility of a lesion in the region of the left cerebellopontine angle. On the seventeenth hospital day lumbar laminectomy was carried out. Multiple subarachnoid cysts were removed and a lumboperitoneal shunt was established. By histopathologic examination, the cysts were found to be cysticerci of Taenia solium

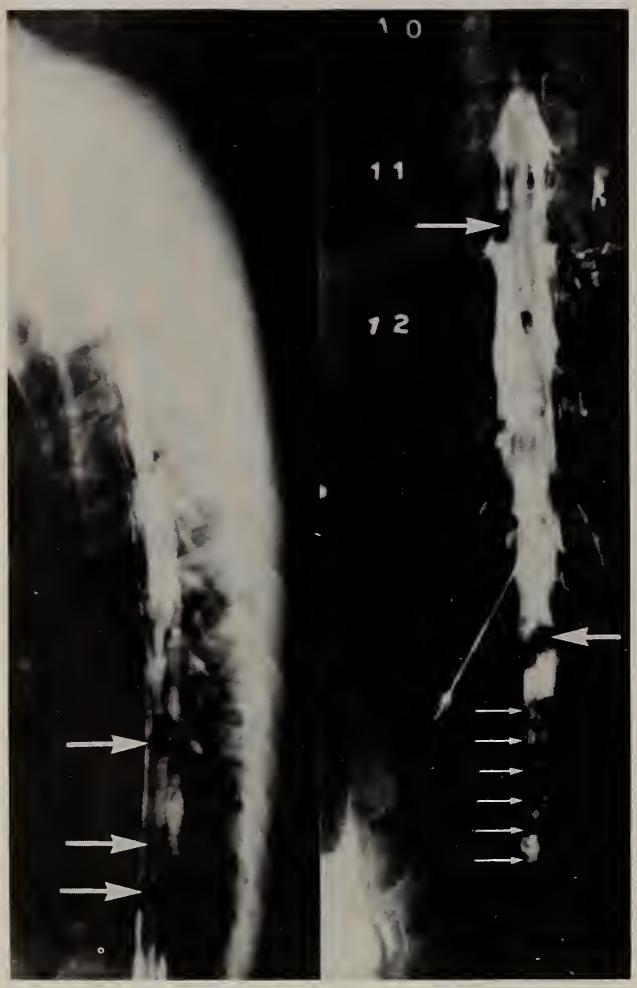


Figure 1.—Lateral and anteroposterior views of myelogram showing tumor-like defects.

Figure 2.—Saggital section of cysticercus of Taenia solium removed at surgical operation. Expanded from ×9.6 using hematoxylin-eosin stain.

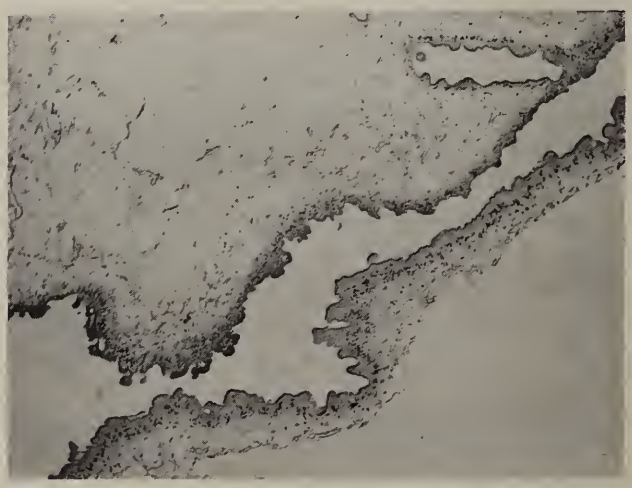


Figure 3.—Higher magnification (x 320) of cuticle from cysticercus of Taenia solium characteristic wart-like projections of cuticle.

(Figures 2 and 3). The cysticercal indirect hemagglutination titer of the patient's serum was subsequently reported as positive at a dilution of 1: 2,048. Cerebrospinal fluid titers were not run.

The patient and immediate relatives were advised of the definitive diagnosis. The importance of medical observations following the initial discharge from the hospital was stressed. In spite of the use of an interpreter and several sessions of explanation, the family refused to believe the diagnosis, and the patient was lost to follow-up.

Discussion

Pigs are the normal intermediate hosts of Taenia solium; human involvement may occur by two means: (1) larvae may be ingested in infected, undercooked pork resulting in the growth of an adult tapeworm in the human gut and (2) ova may enter by way of food or drink contaminated with human feces, or autoinfection may occur in the person harboring Taenia solium by regurgitation of intestinal contents into the stomach.[5] By the second method humans may become infected with the larval stages, which can be found in muscles, as well as brain, skin and eyes. Clinical manifestations vary with the location of the parasites; when infection involves the central nervous system, epilepsy, transient pareses, intermittent obstructive hydrocephalus, dysequilibrium, meningoencephalitis, involuntary movements, failing vision and mental disturbances have been reported.[4] Reports of spinal cysticercosis are exceedingly rare;[9,10] thus, of 450 cases of cysticercosis in British soldiers, only two cases involved the spinal cord.[7] Hesketh reported cysticercosis of the dorsal cord mimicking tumor and diagnosed only at surgical operation.[9] Laboratory studies are of little help in making a diagnosis; cerebrospinal fluid and peripheral blood eosinophilia may be present. On roentgenography, calcified cysts in the soft tissues and brain may be noted.[5]

The intradermal and complement fixation tests for cysticercosis have not received wide acceptance because of their reported unreliability in proven cases.[6,7] Two immunological tests, somewhat more recently developed, appear to be more reliable.[2,3] These are the precipitin ring test and indirect hemagglutination test. Findings on both have been reported positive even at high dilutions of serum, although selection of the antigen source may be critical in determining the sensitivity.[2] Although positive reactions using cerebrospinal fluid have been reported with the precipitin ring test in proven cases,[2] the indirect hemagglutination reaction has been reported less satisfactory using cerebrospinal fluid.[2] The techniques for the serological tests are reported elsewhere.[2,3]

In our patient, cerebrospinal fluid had all of the features of tuberculous meningitis including low glucose, high pressure and protein, and mononuclear pleocytosis. There also was a history suggestive of previous tuberculous disease and during the course of the illness, papilledema and mental changes developed suggesting cerebrospinal fluid block. Myelographic findings indicated spinal cord tumors, thought to be neurofibromas. Although epilepsy is a common manifestation of central nervous system cysticercosis,[1,4-6,7,11] there was no history of seizures in this patient. Possibly the strange episode of paralysis and the unusual meningitis several years earlier represent symptoms of parasitic infection. Epilepsy has been reported as a sequela to cerebral cysticercosis.[8] Although proof is lacking, epilepsy reported in the brother of our patient may have been due to cysticercosis.

In summary, our patient has an extremely rare form of a disease which is common in the country of his origin. The diagnosis was made at surgical operation, after an exhaustive battery of investigations was unhelpful. Physicians confronted with perplexing central nervous system disorders in persons from parts of the world in which T. solium infection is endemic would be well advised to include cysticercal serologic testing early in the evaluation of such patients.

REFERENCES

1. Faust EC, Russell PF, Jung RC: Craig and Faust's Clinical Parasitology, 8th Ed. Philadelphia, Lea & Febiger, 1970, p 529

2. Biagi FF, Tay J: A precipitation reaction for the diagnosis of cysticercosis. Am J Trop Med Hyg 7:63-65, Jan 1958

3. Biagi FF, Navarrete F, Piña A, et al: Estudio de tres reacciones serologicas en el diagnostico de la cisticercosis. Rev Med Hosp Gen (Mexico City) 24:501-508, Nov-Dec 1961

4. Bickerstaff ER: Cerebral cysticercosis: Common but unfamiliar manifestations. Br Med J 1:1055-1058, Apr 30, 1955

5. Brailsford F: *Cysticercus cellulosae*—Its radiographic detection in the musculature and the central nervous system. Br J Radiol 14:79-93, Mar 1941

6. Dixon HBF, Hardgreaves WH: Cysticercosis *(Taenia solium)*—A further ten years' clinical study, covering 284 cases. Q J Med 13:107-121, Oct 1944

7. Dixon HBF, Lipscomb FM: Cysticercosis—An analysis and followup of 450 cases. Med Res Counc Spec Rep Ser (Lond), Ser 299, 1961, pp 58

8. Heinz HJ, MacNab GM: Cysticercosis in the Banta of Southern Africa. S Afr J Med Sci 30:19-31, Jul 1965

9. Hesketh KT: Cysticercosis of the dorsal cord. J Neurol Neurosurg Psychiatry 28:445-448, Oct 1965

10. Kahn P: Cysticercosis of the central nervous system with amyotrophic lateral sclerosis: Case report and review of the literature. J Neurol Neurosurg Psychiatry 35:81-87, Feb 1972

11. White JC, Sweet WH, Richardson EP: Cysticercosis cerebri—A diagnostic and therapeutic problem of increasing importance. N Engl J Med 256:479-486, Mar 14, 1957

Refer to: Jacobson LB: T wave sensing during temporary demand pacing. West J Med 123:314-315, Oct 1975

T Wave Sensing During Temporary Demand Pacing

LESTER B. JACOBSON, MD
San Francisco

TEMPORARY TRANSVENOUS ENDOCARDIAL PACING has proven to be an effective and safe therapeutic method for the management of transient cardiac conduction abnormalities and arrhythmias. While most of the external pacing units available can be used in either fixed rate or demand (R wave inhibited) modes, the latter is usually preferred as it minimizes the possibility of a stimulus falling in a QRST complex where it might initiate repetitive ventricular beating. However, use of the demand mode which depends on the sensing of QRS complexes may be complicated by sensing of deflections other than the QRS complex which may recycle the pacemaker so that a slower than expected escape interval or pacing rate occurs. This report presents an example of T wave sensing resulting in a pacing rate too slow to suppress ventricular ectopic beats.

Report of a Case

A 53-year-old man, a physician, was admitted to hospital with an acute inferior wall myocardial infarction. Over a 12-hour period, atrioventricular (AV) conduction changed from normal PR interval to a prolonged one, to Wenckebach second degree AV block, and then to third degree AV block with a narrow QRS rhythm (almost identical in contour to the earlier sinus QRS rhythm) at a rate of about 45 to 50 beats per minute. With the slow ventricular rate, chest pain recurred, hypotension followed, frequent ventricular ectopic beats and brief runs of ventricular tachycardia appeared and the patient became disoriented.

A 5 F bipolar pacing catheter with electrodes 2.8 cm apart was introduced percutaneously into the right femoral vein and positioned fluoroscopically and electrocardiographically into the right ventricular apex.[1] Stable demand pacing was initiated with a threshold current of about 0.7 milliampere (ma) using the Medtronic Model 5840 external pacemaker in the demand mode with the input sensitivity control (ISC) turned to about a 4 o'clock position (Figure 1). A pacemaker rate of about 72 was selected in order to achieve overdrive suppression of the ventricular ectopic beats,[2] but when the pacer was turned on the rate was noted to be about 52 and the ventricular ectopic beats were occurring intermittently. Since the interval from the peak of the T wave to the next pacing stimulus of about 83 hundredths of a second corresponded to a heart rate of about 72 beats per minute, it was felt that T wave sensing was occurring (Figure 2). Turning the input sensitivity control from a position of about 4 o'clock to 2 o'clock abolished T wave sensing, the heart rate abruptly rose from 52 to 72, and the ventricular ectopic beats disappeared. Demand pacing at this rate was continued for ten days until AV conduction returned with Wenckebach periods and then 1:1 conduction with normal PR intervals. His's bundle electrogram recorded from the pacing catheter as it was withdrawn from the RV apex showed a mildly long A-H time of 124 milliseconds and a normal H-V time of 43 milliseconds. The patient was discharged from the hospital ten days later feeling quite well.

Figure 1.—Medtronic Model 5840 pacemaker with the input sensitivity control (ISC) located in about 4 o'clock position, the heart rate conrol at about 72 beats per minute, and the current at 1 milliampere.

From the Department of Medicine, Cardiovascular Division, University of California, San Francisco.

This paper was supported in part by USPHS, NHLI Clinical Cardiology Training Grant HL 5740.

Submitted March 3, 1975.

Reprint requests to: Lester B. Jacobson, MD, Cardiology Division, Pacific Medical Center, P.O. Box 7999, San Francisco, CA 94120.

Discussion

T wave sensing by external demand pacemakers during temporary endocardial pacing is reportedly a rare event.[3-6] Its infrequent occurrence is attributable to pacemaker design specifications which require a deflection to be of a particular magnitude for it to be sensed, and to the fact that voltage of a T wave is generally much less than that of its QRS complex. Some pacemakers further attempt to prevent T wave recognition by sensing large deflections only if their slope is very rapid, or by having a sensory refractory period of specified duration following each complex sensed or each pulse generated.[7] Despite these safeguards, however, T wave sensing may occur.[3-6]

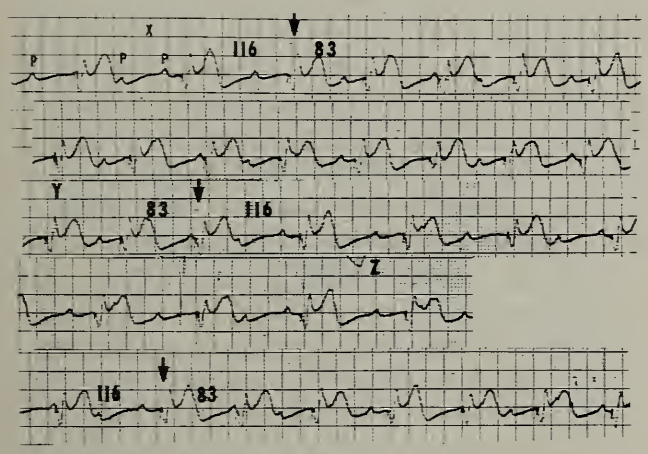


Figure 2.—Five continuous strips of a modified precordial lead. The atrial rhythm is sinus with identical P waves occurring regularly at a PP interval of 48 hundredths of a second (rate 125). Each QRS complex is initiated by a pacemaker artifact and is wide (greater than or equal to 12), indicating that the ventricle is being paced. Third degree (complete) atrioventricular block is established by the presence of only paced QRS complexes despite multiple opportunities for the P wave to capture the ventricles. The intervals between pacer artifacts are either 116 or 83 hundredths of a second, despite the fact that the rate is set for an RR interval of about 83. The interpacer interval at the left of the top strip is 116 hundredths of a second with the input sensitivity control (ISC) positioned (Figure 1) at about 4 o'clock where the sensing circuit can detect deflections of about 2 millivolts (mv) in amplitude. At point X, this control is turned counterclockwise to a position of about 2 o'clock (where deflections must be about 3 mv in amplitude to be sensed) at which time the pacer interval becomes 83 hundredths of a second, which corresponds to the selected pacing rate. At point Y the ISC is moved just a bit clockwise and again the interpacer interval increases to 116 hundredths of a second, while the reverse maneuver at point Z again shortens the interval. The difference between pacing intervals of 33 hundredths of a second (116 minus 83) is just about the interval from the pacer spike to the peak of the T wave, and suggests that the pacemaker sensed the T wave and recycled at that time.

The Medtronic 5840 external pacemaker unit used in the instance presented here, when used in the demand mode, has a refractory period of about 200 milliseconds and a sensing circuit with variable input sensitivity which is selected by the physician (Figure 1).[8] This sensing circuit responds to deflections at the pacemaker terminals of about 2 millivolts (mv) when the dial is at the full clockwise position, and to about 4 mv when it is in the straight upright position. In this patient a deflection occurring about 330 milliseconds after the onset of a pacer spike must have had a voltage of greater than 2 mv and was, therefore, sensed. Although bipolar recording from the catheter tip was not done, this time interval corresponded to the peak of the T wave on both the surface electrocardiogram (Figure 2) and a unipolar electrogram recorded from the distal catheter electrode. And, while sensing of the pacemaker afterpotential could conceivably have caused recycling, this phenomenon is very unlikely to occur with a pacing current of only 1 milliampere and a catheter electrode separation of 2.8 cm.[9] The fact that simple counterclockwise movement of the input sensitivity control rectified the problem also supports the contention that a T wave of unusually high voltage was being sensed.

While T wave sensing resulting in slowing of pacing rate may be of little clinical significance, it may have rather dramatic detrimental effects. In overdrive suppression of ventricular ectopic beats and in the treatment of low cardiac output states in patients with slow heart rates (operating on a flat portion of a Frank-Starling curve), the sudden onset of T wave sensing causing a 28 percent reduction in heart rate as in the case presented here could permit the appearance of serious ventricular arrhythmias or a dramatic drop in cardiac output.

REFERENCES

1. Gulotta SJ: Transvenous cardiac pacing. Circulation 42:701-718, 1970
2. Escher DJW: The treatment of tachyarrhythmias by artificial cardiac pacing. Am Heart J 78:829-832, 1969
3. Castellanos A Jr, Maytin O, Lemberg L: Pacemaker-induced cardiac rhythm disturbances. Ann NY Acad Sci 167:903-910, 1969
4. Barold SS, Gaidula JJ, Lyon JL, et al: Irregular recycling of demand pacemakers from borderline electrographic signals. Am Heart J 82:477-485, 1971
5. Barold SS, Kelley JW: Sensing problems with demand pacemakers, *In* Samet P (Ed): Cardiac Pacing. New York, Grune and Stratton, 1973, pp 385-412
6. Siegel FA, Hsu I, Borth DD: Temporary transvenous pacemaker monitoring using simultaneous endocardial and surface electrocardiograms. Chest 62:286-291, 1972
7. Berkovits BV: Demand pacing. Ann NY Acad Sci 167:891-895, 1969
8. Technical Information TC 67059: Medtronic Demand Pacemaker Model 5840. Minneapolis, Medtronic, Inc., May 1967
9. Barold SS, Carroll M: "Double reset" of demand pacemakers. Am Heart J 84:276-277, 1972

LETTERS *to the Editor*

Sleep Apnea

To the Editor: In the article "Sleep Apnea Syndrome" (West J Med 123:7-16, Jul 1975) I missed Cheyne-Stokes breathing and its preventive treatment. If it leads to sleep apnea, this periodic respiration is due to diminished sensitivity of the respiratory center in the medulla caused by lack of oxygen. It is seen most frequently in arteriosclerotic and hypertensive patients in advanced stages of their cardiovascular disease. Aminophyllin intravenously is the remedy of choice and acts by stimulation of the respiratory center, whereas barbiturates and other sedatives are without avail and morphine is strictly contraindicated. The stimulating action of aminophyllin upon the respiratory center, if injected intravenously, was first discovered and therapeutically used in 1927 by my former assistant A. Vogel.[1]

Julius Bauer, MD
Beverly Hills

REFERENCE

1. Vogl A: Erfahrungen ueber Euphyllin bei Cheyne-Stokes und anderen Formen centraler Atemstoerung. Med Klin No. 1; 1932. *Cited In:* Bauer J: Differential Diagnosis of Internal Diseases, 3rd Ed. Grune and Stratton, 1967, p 283

On Informing the Patient

To the Editor: During this unhappy period of widespread distress concerning insurance coverage and the potentials of being sued, the profession has had to face more than usual criticism. Even though much of the criticism does not seem to be factually founded or justified, one wonders whether some good might be derived from this display of public complaints. Despite the necessity of having to accept that in some instances some physicians have failed to conduct their activities in the best interests of their patients, the profession as a whole should not be jockeyed into a defensive position. Yet under these circumstances it seems reasonable for the profession to "take a look in the mirror" and to ask if there are some aspects of the manner in which modern clinical practice is conducted that might be contributory to present miseries and if there are changes that can be made for improvement.

For several decades the public has been avalanched with medical and scientific information and because it is avidly received the media provide more and more. "Public education" of this type may be good in its ultimate, but since the information thus presented is superficial it tends to stir personalized interest without providing bases for judgment. Nevertheless, "Mr. John Doe" has learned to ask questions, to assume a doubting attitude and to expect answers. The query the profession might consider from its "view in the mirror" is whether it has kept pace with the public by being willing to take the time to answer questions and to explain the circumstances medically. Explanation and full discussion with patient and family have always been recognized and utilized by the physician as good supportive therapy since it is the direct means of allaying anxiety and unjustified fears. But it would seem that John Doe's attitude, which nowadays is so different from the old—"doctor knows best"—tends to cause practitioners to remain aloof and sometimes, almost wordless—until all the test results are in!

Those of us in academic medicine—cloistered in the proverbial "ivory towers"—can be as inadequate or even more so in this type of communication with patients than are those in private practice. Additionally, academic medicine may well have failed to keep pace with the changing times by not including designed instruction by example or otherwise in how and when to deliver medical information to the patients and their families.

From the point of view of an academic consultant in a medical specialty, a frequent statement heard from patients and their families is some variation of "Gee, why didn't the doctor tell me?" Recently, this consultant was told more specifically: "If the doctor had been more willing to talk about my wife's problem, I would not have discussed the situation with my attorney!" Hopefully, no suit will follow in this instance for nothing professionally wrong occurred, unless inadequate communication between doctor and patient will be construed as malpractice.

The total circumstances of the present regarding patient-doctor relationships are far too complex to bring down to one simple explanation. However, if there be one, the "Achilles heel" of

modern medical practice might reasonably be considered to be in the failure of the physician to provide information to those who are concerned as it develops.

AUGUSTUS S. ROSE, MD
Professor Emeritus, Neurology
University of California, Los Angeles
School of Medicine

Withholding of Physicians' Services

TO THE EDITOR: I enjoyed your editorial essay "On the Withholding of Physicians' Services" [West J Med 123:136-138, Aug 1975] far more than mere words can express to you. There are many of us who are appalled at the callousness of doctors who went on strike. Any good that we were accomplishing in terms of public image and legislative goals was by that action badly compromised, if not negated.

Even the most conservative of us must admit that the tripling or quadrupling of premiums had created a crisis. The real point of the problem was why had this not been anticipated by our leaders? I know that you, among others, have been aware for a long time of the precarious fiscal position of our professional liability carriers in regards to this segment of their business operation. It seems to me that for at least four to five years organized medicine has been stalling and not really addressing itself to the basic issues of the rising incidence of claims and their source in the attitude of the public, not the increased incidence of physician error.

This was actually more of a social than an insurance or medical care problem, as we all know.

Thank goodness there will be some tort remedies and I am happy to join with you in the approach that you have taken.

HOMER C. PHEASANT, MD
Los Angeles

"Gurney" Again— Scots Origin Theory Scotched?

TO THE EDITOR: The suggestion of Dr. J. B. deC. M. Saunders (West J Med 122:515-516, Jun 1975) that the word "gurney" derives from the Scots verb "girn" (meaning to groan in pain, to complain persistently, etc.) appealed very much to my sentimental Celtic (Welsh) nature. However, his assertion that "the word gurney for a wheeled stretcher is common in Scotland and the North of England" was harder for me to swallow because I once worked in a hospital in the North of England and never once heard the word.

Therefore, I recently appealed to the faculties of Scottish university medical schools for information and I have now received replies from Aberdeen,[1] Dundee,[2] Edinburgh[3] and Glasgow.[4] The answers reveal that although "girn" does mean to complain persistently, "gurney" is unknown in Scotland. It is certainly not used to describe a wheeled stretcher; in Scotland, as in England, such a conveyance is known as a trolley.

It seems to me that the best present theory is still that "gurney" was somehow derived from the gurney cab or bus.[5,6]

Further support of this idea is contained in a 1966 article recently brought to my attention by its author, P. Tamony.[7] Apparently, a gurney was a horse-drawn rear-entrance cab with two seats set longitudinally, facing each other. It was named after its inventor, J. Theodore Gurney of Boston who was granted a United States patent for it in 1883.

At the end of the 19th century Gurney Cab companies existed in both San Francisco and Oakland. One can probably assume that they were so named after the type of cab which they used (at any rate, the proprietors of the Oakland company were named Kane and Daly). A Gurney Cab Company operated in Vancouver as well and there too, it seems, the word came to be applied to the wheeled stretcher.[8]

According to Tamony, San Francisco police wagons and ambulances came to be known as gurneys, presumably because they also had rear entrances. So perhaps it was only a small jump to apply the word to any wheeled vehicle designed to carry a sick or injured person.

DAVID VERNON THOMAS, MD
Los Altos

REFERENCES

1. Baird DA, Executive Dean, University of Aberdeen School of Medicine: Personal communication, July 25, 1975
2. Brown AJG, Secretary of the Faculty of Medicine, University of Dundee: Personal communication, Aug 8, 1975
3. Adams JA, Librarian, University of Edinburgh Medical School: Personal communication, Jul 7, 1975
4. Haddow AJ, Administrative Dean of Medicine, University of Glasgow: Personal communication, Jun 26, 1975
5. Frishman D: Some wonderment on a word, *In* Bayland, San Francisco Examiner, Feb 17, 1959
6. Edwards RF: That word "gurney" (Letter to Editor). West J Med 122:515, Jun 1975
7. Tamony P: A San Francisco word goes national. The Pacific Historian, 10:15-20, 1966
8. Majke D via Kay MW, Joint Editorial Director, G & C Merriam Co, Springfield, Mass: Personal communication

A "Medical Grange" for Malpractice Insurance

To the Editor: The Medical Grange—a system for survival in the malpractice insurance crisis?

Professional liability coverage, in the form of insurance, is an invitation to a suit. Malpractice attorneys and juries tend to regard insurance as an amorphous pot of gold. Since the doctor has already placed the money into the pot, they reason, he isn't being hurt when it is drained. No matter who the owner is—be it Travelers, Argonaut or even the CMA—this concept of an insurance pot will not change. Somehow we must find an alternative to professional liability insurance which will protect physicians from serious economic loss, be reasonably priced to avoid a fee increase and allow the injured patient to be compensated adequately. All this with no consideration to the effects of legislative reform, as it may well be two to five years before such reforms become law.

By reviewing how the professional liability insurance premium is spent, we can perhaps determine a *new* approach to liability protection.

1. Insurance company overhead—34 percent. This pays the salaries, taxes and profits of the company. CMA-sponsored insurance may be able to reduce this to 25 percent, which is hardly a savings. So, we eliminate the insurance company completely by *canceling our insurance.*

2. Defense attorney fees—38 percent. Most suits are not based on malpractice incidents, yet *all* must be defended. Under the current system, it frequently takes years to settle the suit, with defense costs rising as the legal chess game continues. The answer here is twofold: (a) binding arbitration agreements with our patients and (b) a group coverage system with a $10,000 deductible feature.

Binding arbitration has been shown to be effective in eliminating nuisance suits' costs. Rapid arbitration settlement promotes greater patient satisfaction and lessens the tendency to seek vindictive and punitive awards. The $10,000 deductible clause would take the bulk of the defense attorney fees off the shoulders of the group and place it directly upon the doctor being sued. Almost all doctors can afford a $10,000 loss, but cannot afford the $50,000 or $1,000,000 settlement. We need protection in the area *over* $10,000 and really not below that amount.

Therefore, by eliminating the insurance company (34 percent), and by reducing and moving defense fees (38 percent) to the pocket of the defending physician, we have eliminated 72 percent of the cost of the professional liability coverage. The remaining 28 percent goes to patients (16 percent) and their attorneys (12 percent).

In tribute to the early West when mutual protective groups were mandatory for survival, this concept can be called the Medical Grange. Here is how such a group could work:

1. Carefully select one thousand (1,000) physicians with similar attitudes to quality medical practice and with a minimum of bad risk practices.

2. Each Grange member would cancel his professional liability insurance, and notify his patients of the same, and secure binding arbitration agreements. Patients do prefer binding arbitration to a 25 to 35 percent increase in medical fees.

3. Each physician will pledge to his fellow Grange members to establish and maintain a $10,000 self-defense fund in his own name and control. This self-defense fund would be his deductible amount to be used only for defense attorney fees or awards. Each year the physician would add another $2,000 to his self-defense fund until it reached $20,000.

4. At the start of the program each of the one thousand physicians would contribute $4,000 apiece as a performance bond to the Grange fund. This fund of $4,000,000 would be invested at 8 percent interest, and the $320,000 interest would pay the salaries of the administrator, clerical staff, meetings, publications, correspondence and the retaining fees of the defense counsel. Every year each Grange member would add another $1,000 to the Grange fund.

5. When a member is successfully sued, he would pay the first $10,000 of costs and awards and the remainder would be spread out over the group of one thousand. This assessment would be prorated according to the risk of the specialty of the individual member. If a member failed to pay his assessment within a given period of time, he would lose his Grange membership and coverage and the assessed amount would be subtracted from his performance bond.

6. If and when less expensive malpractice insurance becomes available, that is, via national health insurance, the Grange fund will be returned to the members and the Grange will be dissolved.

In 1974 among 40,000 physicians in California, $34,000,000 was awarded to the patients and

their attorneys. This is the 28 percent of the premium dollar. Assuming that awards do not decrease and that the one thousand Grange members have average performance and risk, the cost to the individual non-sued member would have been $850. This is a far cry from the premiums most of us pay at the present time.

Undoubtedly, there are many aspects of this Grange concept that need to be clarified and solved. But the legal framework *can* be developed. It is time that we explore *all* alternatives, and there is no reason that physicians themselves cannot develop a new system. Do we have to wait for someone else to do what we need done for ourselves? I would enjoy your comments and suggestions.

HARVEY E. KNOERNSCHILD, MD
San Jose

Diabetic Microangiopathy

TO THE EDITOR: It has come to our attention that in a Medical Staff Conference on Diabetic Microangiopathy (West J Med 121:404-412, Nov 1974) Dr. Marvin Siperstein took rather questionable liberties with the statistics of data published by Dr. Paul Beisswenger and one of the undersigned (R.G.S.) on the composition of diabetic glomerular basement membrane.[1]

Dr. Siperstein claimed that the observation of a statistically significant elevation ($P<0.01$) of the hydroxylysine content of diabetic basement membranes depends entirely on the highest point in the group of eight diabetic cases and that omission of this point leads to a nonsignificant P value.

A careful statistical reanalysis of these data has indicated that Dr. Siperstein's contentions are unfounded and incorrect. The highest value of the diabetic cases does not meet the criteria for an "outlying observation"[2] and therefore can not be rejected. Indeed even when this highest number is excluded, a comparison of the normal and remaining diabetic cases still shows a significant difference ($P<0.02$). If Dr. Siperstein had been motivated to leave out the lowest rather than the highest diabetic point, which is equally unjustifiable, a P value of less than 0.005 between the two groups would have been obtained.

In a further attempt to detract from the data, Dr. Siperstein indicated that five of the eight diabetic cases are within normal limits ($\pm 2SD$). In fact this observation has no adverse implications since it only indicates that the groups overlap. Such overlapping frequently occurs between different groups, but it is the standard error of the mean which is utilized in determining whether or not the samples come from a single or two distinct populations.

In his presentation Dr. Siperstein fails to mention the additional compositional changes observed in the diabetic glomerular basement membrane[1] such as the decrease in lysine ($P<0.001$), increase in glucose ($P<0.01$) and increase in galactose ($P<0.001$).

The question of the relationship of control to the microvascular complications is one which is of great importance to practitioners and researchers in the field of diabetes. There is no general acceptance of Dr. Siperstein's statement that "It is now apparent to everyone who follows diabetic patients that these manifestations of diabetes progress rather inexorably, regardless of the degree of control." It is unfortunate that in his zeal to advance his point of view, Dr. Siperstein finds it necessary to distort not only this work of Beisswenger and Spiro but also the distinguished contributions of Williamson and of Bloodworth and Engerman.

ROBERT G. SPIRO, MD
Professor of Biological Chemistry

RAY E. GLEASON, PH D
Principal Associate in Medicine (Mathematical Biology)
Harvard Medical School
Joslin Research Laboratory, Boston
Boston, Massachusetts

REFERENCES

1. Beisswenger PJ, Spiro RG: Studies on human glomerular basement membrane—Composition, nature of the carbohydrate units and chemical changes in diabetes mellitus. Diabetes 22: 180-193, Mar 1973
2. Grubbs FE: Procedures for detecting outlying observations in samples. Technometrics 11:1-211, 1969

* * *

The Author Replies

TO THE EDITOR: In my grand rounds of January 9, 1974 on diabetic microangiopathy [Medical Staff Conference. West J Med 121:401-412, Nov 1974], I discussed, and tried to put into perspective, the finding of an increase in hydroxylysine in diabetic basement membranes, which has been reported by Drs. Beisswenger and Spiro.[1,2] In their writings, Dr. Spiro and Dr. Beisswenger have emphasized that they have found "marked" and "consistent" increases in the *hydroxylysine* con-

tent of diabetic basement membranes.[3,4] These conclusions have understandably led to a widespread belief that such changes in basement membrane hydroxylysine levels may represent the biochemical basis for diabetic microangiopathy.

In my discussion of this finding, I first clearly stated that "there is indeed a statistically significant difference in the mean hydroxylysine values, of the eight diabetic and eight normal basement membranes." Regardless of the statistical significance of this difference, however, it is important from the standpoint of their physiologic significance to point out that the differences reported were neither so "marked" nor so "consistent" as these authors have stated in their publications. The difference in hydroxylysine content of the diabetic and normal groups averaged only 19 percent; and by omitting the one highest diabetic value two standard errors from each mean do overlap. Nonetheless, Dr. Spiro is absolutely correct in pointing out that this small difference in the means remains statistically significant ($P<0.02$) even when the highest diabetic point is omitted.

Secondly, however, I emphasized the inconsistency of the hydroxylysine data by pointing out that only three of the eight diabetic patients studied had basement membrane hydroxylysine values that were outside of the normal range. Quite aside from the difference between the means of the two groups, for a finding to be "consistent" in the eight diabetic patients that Drs. Spiro and Beisswenger studied it would seem apparent that more than *three* of the diabetic patients should show the lesion. If increased hydroxylysine were in fact responsible for the abnormalities in basement membrane that were present in the far advanced lesions examined, it is not unreasonable to ask why the majority, i.e., five of their eight diabetic patients, showed no significant change in basement membrane hydroxylysine content. Dr. Spiro's letter dismisses, but does not dispute this point.

Thirdly, as I also noted in my review, three other laboratories[5-7] have published data that refute the finding of an increase in hydroxylysine in diabetic renal basement membranes. Kefalides[7] concludes: "The results indicate that the slight increases in hydroxylysine and hexose content observed occasionally in diabetic GBM [glomerular basement membrane] preparations are of no statistical significance and cannot be attributed to increases in the activities of enzymes which hydroxylate lysine or glycosylate hydroxylysine, respectively." I believe, therefore, that one is quite justified in concluding, as I did, "that there is simply no solid evidence to indicate *consistent* biochemical change in the primary structure of the basement membrane of the diabetic kidney."

Finally, regarding the inexorable progression of diabetic retinopathy, the point made was simply that the best control does not prevent retinopathy. Whether the rate of progression of the lesion can be influenced by better or poorer control was explicitly and purposely not discussed in this Medical Staff Conference. The point that retinopathy cannot be *prevented* in the vast majority of the diabetics is probably best documented from the data published from Dr. Spiro's institution, which has reported that 90 percent of diabetic patients manifest diabetic retinopathy after the third decade of their disease.[8] In this regard, Oakley et al have recently reported that those few diabetics who do escape retinopathy after 40 years of diabetes had been no better controlled than those who do develop retinopathy.[9] While no one advocates poor control of the diabetic, in view of these data, I doubt whether many clinicians today really believe that the best control that we are capable of delivering to our diabetics really prevents, or even arrests, diabetic retinopathy.

MARVIN D. SIPERSTEIN, MD, PH D
Professor of Medicine
Chief, Metabolism Section
University of California Service
Veterans Administration Hospital, San Francisco

REFERENCES

1. Beisswenger PJ, Spiro RG: Human glomerular basement membrane—Chemical alteration in diabetes mellitus. Science 168: 596-598, May 1, 1970

2. Beisswenger PJ, Spiro RG: Studies on the human glomerular basement membrane—Composition, nature of the carbohydrate units and chemical changes in diabetes mellitus. Diabetes 22: 180-193, Mar 1973

3. Spiro RG: Biochemistry of the renal glomerular basement membrane and its alterations in diabetes mellitus. N Engl J Med 288:1337-1342, Jun 1973

4. Beisswenger PJ: Specificity of the clinical alteration in the diabetic glomerular basement membrane. Diabetes 22:744-750, Oct 1973

5. Lazarow A, Speidel E: The chemical composition of the glomerular basement membrane and its relationship to the production of diabetic complications, *In* Siperstein MD, Colwell AR Sr, Meyer K (Eds): Small Blood Vessel Involvement in Diabetes Mellitus. Washington, D.C., American Institute of Biological Sciences, 1964, p 127

6. Westberg NG, Michael AF: Human glomerular basement membranes—Chemical composition in diabetes mellitus. Acta Med Scand 193:39-47, Jul-Aug 1973

7. Kefalides NA: Biochemical properties of human glomerular basement membrane in normal and diabetic kidneys. J Clin Invest 53:403, 1974

8. White P: Childhood diabetes—Its course, and influence on the second and third generations. Diabetes 9:345, 1960

9. Oakley WG, Pyke DA, Tattersall RB, et al: Long-term diabetes—A clinical study of 92 patients after 40 years. Q J Med New Series, 43:145-156, Jan 1974

Trauma Rounds

Chief Discussant
ROBERT C. LIM, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Lim RC: Abdominal vascular injuries (Trauma Rounds). West J Med 123:321-324, Oct 1975

Abdominal Vascular Injuries

WILLIAM COPELAND, MD:* The patient is a 16-year-old Latin American girl who was admitted with a self-inflicted gunshot wound of the right epigastrium. The exit wound was above the left iliac crest posteriorly. When first evaluated in the emergency room, blood pressure was 130/80 mm of mercury and pulse was 110 and regular. However, peripheral perfusion was decreased as shown by cool, pale extremities. Sensorium was intact. No abnormalities were noted on initial urinalysis and the urine was found to be without red cells. After placement of a large-bore cutdown and rapid infusion of Ringer's lactate solution, the patient was moved to the x-ray department so that films of the chest and abdomen could be made. The film of the chest showed no abnormalities. During the radiological examination an expanding mass in the left lower quadrant was noted and films of the abdomen confirmed this.

Immediate exploration of the abdomen showed the following injuries (1) a through and through laceration of the right gastroepiploic artery and vein, (2) a through and through wound of the third portion of the duodenum, (3) a wound of the infrarenal aorta approximately 1 cm in size with extensive retroperitoneal bleeding. The bullet exited through the left psoas muscle, lacerating a lumbar artery. Proximal and distal control of the aortic injury was obtained and the laceration was sutured with running 4-0 vascular suture. The gastroepiploic artery was ligated and the duodenal wounds were closed with a double layer technique. The duodenum was decompressed with a 10 Foley catheter duodenostomy.

The estimated blood loss was 5 units of whole blood. Six units of whole blood were replaced. The postoperative course was relatively uneventful and the duodenostomy was removed on the ninth postinjury day. The patient was discharged on the eleventh postinjury day.

DONALD TRUNKEY, MD:† *We have asked Dr. Robert Lim, Associate Professor of Surgery and Chief of our Emergency Department, to discuss the management of vascular injuries of the abdomen.*

Dr. Lim, this case does not represent the typical large vessel injury we see because the patient was in compensated shock when she arrived. But using her as the focal point, would you discuss these injuries?

ROBERT C. LIM, MD:‡ I would like to begin the discussion by pointing out the relative frequency of this type of injury. In 1972 we reviewed all

*Intern, Trauma Service, San Francisco General Hospital.

Sponsored by the American College of Surgeons Northern California Trauma Committee. Supported in part by NIH Grant GM18470.

Reprint requests to: Donald D. Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco CA 94110.

†Assistant Professor of Surgery, San Francisco General Hospital.

‡Associate Professor of Surgery, and Chief of Mission Emergency Service, San Francisco General Hospital.

trauma deaths in San Francisco. Of these, 150 patients (35.2 percent) died from injuries resulting from hemorrhage. Eight were secondary to either blunt or penetrating wounds of the aorta.

We were stimulated by these statistics to review those major aortic injuries which reached San Francisco General Hospital. In the last five years there were 32 patients who survived their injury long enough to reach the emergency room. All but three of the patients presented at the emergency room in profound shock. Half had dilated fixed pupils and no palpable blood pressure. I should add parenthetically that we do not consider an unobtainable pressure and fixed dilated pupils as a sign of an irreversible injury. In the past year we have successfully resuscitated eight such patients and only one had significant neurological residual.

In reviewing the 32 aortic injuries treated at San Francisco General, we divided them into three major groups: injuries to the diaphragmatic aorta, the suprarenal aorta and the infrarenal aorta. Roughly half of those patients with injuries of the diaphragmatic aorta or infrarenal aorta survived but only 11 percent of patients with injuries of the aorta between the celiac artery and renal arteries lived. This is because associated injuries of one or more of the important structures, such as pancreas and liver, in this area are common and contribute to the very high mortality. Associated injuries are the rule in all aortic injuries, and most of our patients had accompanying injuries of the bowel, mesentery and solid organs.

First, I would like to comment on the resuscitation of any patient who presents in profound shock. Large bore cutdowns in multiple sites (basilic vein of the arm and saphenous vein of the ankle) are required. Infusion of balanced salt solution should be begun immediately after blood is drawn for typing and cross-matching. If the patient responds to the fluid resuscitation, further assessment may be carried out. When there has been major abdominal vessel injury the patient usually does not respond and immediate operative intervention is required. As a general rule whole blood administration is not done in the emergency room and is reserved until control of the major bleeding is obtained. Otherwise blood is wasted as it continues to bleed into body cavities and is not available for the final phase of resuscitation. Cardiac surgical experience has shown that patients do well on hemodilution and resuscitation may actually be enhanced. It is not until hemodilution produces an hematocrit below 20 that oxygen carrying capacity is significantly interfered with. Any center dealing with large numbers of trauma patients should maintain reserves of blood of all the common types. The use of type specific blood in a trauma patient receiving massive transfusions is preferable to type O negative blood. We feel this has been a very important point in avoiding some of the minor mismatch problems which are magnified when such a patient receives large quantities of transfused blood.

The case presented today points out another factor necessary for survival. There must be a high index of suspicion at major vessel injury especially when a patient presents in profound shock and does not respond promptly to fluid resuscitation. While major abdominal vascular injury is relatively rare with blunt trauma, it should be suspected when the violence is severe as documented by other associated injuries.

The last point I wish to make in regard to management of these injuries in the emergency room is that with cardiac arrest or arrests during resuscitation we advocate opening the chest with a left sixth interspace thoracotomy incision in order to institute open chest massage and to cross-clamp the supradiaphragmatic aorta. This may permit salvage of what is otherwise a hopeless situation. When the heart is empty or when cardiac tamponade has occurred, closed cardiac massage is futile and more effective circulatory support can be provided through the open chest. The ready accessibility of the descending thoracic aorta through the left chest permits prompt control of intraabdominal arterial bleeding so that volume can be restored and cerebral perfusion ensured. Occlusion of the thoracic aorta will direct whatever blood volume is left towards the heart and brain.

In the group of aortic injuries which we reviewed, all but three of the patients presented to the emergency room in shock. In half the patients, there were cardiac arrests in the emergency room. Open cardiac resuscitation and aortic crossclamping were found to be helpful in resuscitating these patients.

A Physician: *How does a surgeon gain control of the aortic injuries at the various sites?*

Dr. Lim: It will vary depending on the section of the aorta that is injured. If the injury is in the upper abdominal aorta it may be necessary to open into the left chest through the sixth or

seventh intercostal space and gain proximal control of the aorta above the diaphragm. Access to the injury itself is then gained by making an incision along the left lateral peritoneal reflection and mobilizing the left colon, the spleen and the tail of the pancreas towards the right. This will allow exposure of the aorta from the diaphragm to the iliac bifurcation (Figure 1). It may also be necessary to take down part of the crus of the diaphragm to gain access to the very uppermost portion of the abdominal aorta. In injuries to the infrarenal aorta, exposure can be gained by reflection of the left colon alone or by paraduodenal approach, much as one approaches a patient with a ruptured abdominal aortic aneurysm.

A PHYSICIAN: *What about the patient who sustains a major intra-abdominal vascular injury in a remote or rural area and there is no trauma center? What do you do then?*

DR. LIM: In those particular instances there has been interest in investigating the use of the Medical Anti-Shock Trouser (MAST), to slow or stabilize bleeding long enough to permit transport of the patient. These trousers are a three-compartment inflatable suit that fits snugly around the waist and both legs. They are inflatable to 80 mm of mercury. These trousers functionally occlude the aorta at the diaphragm. It is not known at the present time how long these trousers can be left on, but it is safe to say that a patient could certainly tolerate up to an hour of transportation with these pants. The surgeon who is going to remove these pants must be prepared to deal with the consequences of suddenly declamping the aorta.

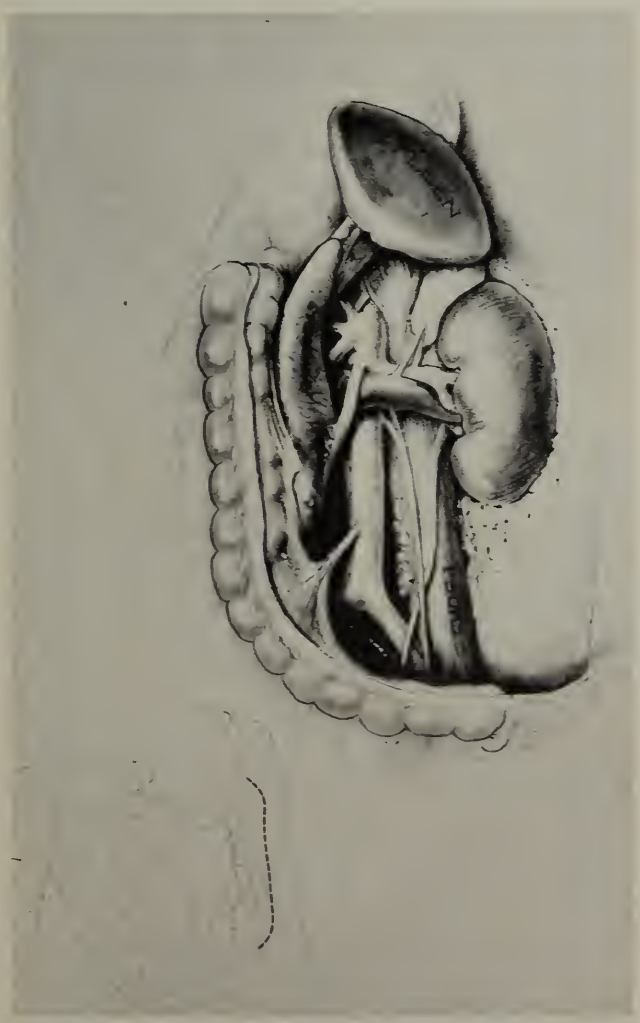


Figure 1.—Rapid exposure of abdominal aorta.

DR. TRUNKEY: *Dr. Lim, would you mention the significance of declamping shock?*

DR. LIM: An entity called hidden acidosis has been described which results from low perfusion in the region supplied by the temporarily occluded aorta. Anaerobic metabolism at the tissue level will lead to accumulation of lactate acid and acid by-products of metabolism in the ischemic tissues which is not reflected in the systemic circulation during the period of vascular occlusion. When circulation is restored by removal of the aortic clamp there is a washout of these acid metabolites into the general circulation and these have profound effects on cardiovascular dynamics. Years ago, we did a number of studies measuring the pH of blood coming from the extremities after aortic occlusion and found the pH was often around 6. This acid load will depress myocardial function when the notably dilated vascular bed is opened up. The anesthesiologist must be ready to administer sodium bicarbonate and infuse fluids rapidly as the clamp is removed. If this is not done profound hypotension due to sequestration of volume in the lower extremity combined with myocardial depression will lead to cardiac arrest.

F. WILLIAM BLAISDELL, MD:* *Dr. Lim, would you like to make a few comments on the management of major venous injury within the abdomen?*

DR. LIM: There is one very important factor that should guide you in the repair of any venous injury in the abdomen. This is the amount and extent of associated injuries. I think we waste too much time trying to repair venous injuries. There are only two that absolutely require repair: the

*Chief of Surgical Service, San Francisco General Hospital.

suprarenal cava and the portal venous system. All other venous injuries within the abdomen may be safely ligated with no untoward sequelae. Ligation is indicated if there are other major injuries such as an aortic injury or major liver or pancreatic injury.

The reason for this is two-fold. Ill advised attempts to repair the vein may lead to further blood loss. In addition, the area of the repair is a potential source for thromboembolic complications. The greater the number of associated injuries, the greater this theoretical hazard. In those venous injuries where there are not extensive associated injuries and the patient is not in shock, then an attempt at lateral repair may be made. I would not do so, however, at the expense of further blood loss which unduly prolongs the operation.

A Physician: *Would you ligate an injury to a renal vein?*

Dr. Lim: Yes. It has been shown in surgical procedures done for portal hypertension and also in other operations dealing with renal veins that ligation of renal veins is well tolerated. The kidney will do quite well as collaterals developed in the capsule. Another major source of collateral venous drainage for the kidney is by the way of the gonadal and adrenal branches.

A Physician: *Does clamping the aorta control venous hemorrhage?*

Dr. Lim: No. Venous bleeding will continue despite crossclamping of the aorta. Major caval injuries will continue to hemorrhage in a retrograde manner just as readily after aortic clamping as before. The best way to gain control of major venous hemorrhage is by packing or direct compression of the injury. The venous system is a low pressure system and judicious use of pressure will temporarily control almost all venous bleeding. We do not routinely advocate use of vascular clamps on venous injuries since they are apt to tear the vein and cause further damage.

In closing, I would like to reemphasize that when one does not know the exact location of an injury to the aorta, rapid exposure of the entire abdominal aorta may be obtained by incising and reflecting the peritoneal attachment of the left colon along with the spleen and tail of the pancreas to the right. If there should be bleeding from the posterior aspect of the aorta, the kidney may be mobilized from its bed and also reflected over to the right. In this way one can secure any posterior injury of the aorta or any tangential injury of the aorta. If difficulty is still encountered in securing the posterior injury one can carry out an anterior aortotomy or enlarge an existing anterior injury so that one can repair the back wall of the aorta from within the lumen.

CORRECTION

In the Article "Manganese Intoxication," which appeared in the August 1975 issue of the Journal, an error in editing was made which indicated that the concentration of manganese in ambient air is 0.1 microgram per cu mm. The second sentence, page 101, should read "The ambient air concentration averages 0.1 microgram (μg) per cubic meter."

Refer to: Eddy JR: Candide becomes a doctor (From a Medical Student). West J Med 123:325-327, Oct 1975

Candide Becomes a Doctor

JOHN R. EDDY, MD, *Stanford*

It has been shown that things cannot be otherwise; since everything was created for a purpose, this purpose must inevitably be the best possible. Observe that noses were made to wear spectacles and so we have spectacles. Legs were obviously intended to wear breeches and so we have breeches. Stones were made to be cut and to be made into mansions. That is why His Lordship has such a very fine mansion. The greatest baron in the province should be the best housed. Pigs were made to be eaten, so we eat pork all the year round. Therefore, people who told us merely that everything was well ordained were talking nonsense. They should have said, "Everything is ordained for the best."[1]

SOME OF YOU will probably attribute this exercise in casuistry to Pangloss, Voltaire's metaphysico-theologo-cosmologist and arch-charlatan, whose verbal veil drops so easily before Candide's ingenuous eyes in the satire of the same name. You are to be congratulated for your scholarly acumen, and pardoned for your error. Rather this catechism was recited to me by a physician and admissions committee member at a prominent institution about five years ago, when I was applying to medical school. Many of my classmates heard in substance the same credo at their various interviews across the country, five years ago and again last year, although I doubt that many of them were as naive as I.

For during that interview, punctuated by the tireless stream of messages over the intercom and patients through the corridors, I began to understand the reasonableness of my inquisitor's characterization of American medicine. Peering through a window on the twelfth floor of that massive but austere edifice in which death and misery were being exorcised with a tirelessly efficient, calculated scientific vigor, unconsciously I had begun to nod my head. There were the people, our patients, myriad specks stretching far below us to the ocean. They live somewhere in that jumbled cityscape which beggars even Cézanne's cubist towns. From that abstract panorama they ascend to our medical fortress. Here, we restore health. Laboratories on the vanguard of technical sophistication relentlessly winnow nature's produce, separating publishable wheat from statistically insignificant chaff. Catheters are placed, fluids are analyzed, organs are investigated with a panoply of probing rays, sensitive fingertips and subtle assays, all eventuating in pharmacologic regimens or surgical operations which purge disease. Healthy, our erstwhile patients return to their cubist mural. Yes, I was beginning to see things perfectly clearly.

Yet there are certain murky thinkers and errant detractors who fail to appreciate the distinctions which alone make possible the flawless operation

An address delivered to the author's classmates on the occasion of their graduation from the School of Medicine at the University of California, Davis, June 6, 1975.

Submitted June 24, 1975.

Reprint requests to: John R. Eddy, MD, Department of Medicine, Stanford Medical Center, Stanford, CA 94305.

of our medical principality. Robert Cook[2] is one. He has investigated the relationship between nutrition and mortality among children less than five years old living in the Caribbean. Although infant mortality rates in these islands ranged from two to four times those in Great Britain, death rates among one-year-olds ranged from 5 to 50 times Britain's rates. To explain these data Cook demonstrates a close inverse correlation between per capita income, used as a measure of nutritional status, and pediatric mortality. Some 20 to 60 percent of eastern Caribbean pediatric beds are occupied by children with intestinal disease due to malnutrition. In 1967 in Jamaica 65 percent of deaths among children six months to three years of age was attributed to malnutrition as the sole or major complicating cause. All told, of the 150,000 children born in the Caribbean in 1969, 3,300 will die in childhood because of malnutrition. And while data availability and diversity of nutritional status recommend the Caribbean area to epidemiologists, conclusions drawn here apply even more pointedly to sub-Saharan Africa, to parts of India, to Bangladesh, to southeast Asia and to many regions in Central and South America.

The toll from malnutrition is probably greater among the living than the dead. Studies from Serbia,[3] Britain,[4] Peru,[5] the United States[6] and India[7] show diminished intelligence among populations chronically malnourished during childhood, compared with control groups matched for age,[3-7] sex,[4-7] race,[5-7] birthweight,[6] socioeconomic status,[5-7] family size,[5-7] birth order[7] and parental education.[5,7] M. J. Begab[8] at the National Institutes of Health estimates that 11 million, or about 3 percent of children in developing countries, are symptomatically undernourished. And while he diplomatically observes that short-term undernourishment of children and mothers in eastern Europe during World War II did not lower the mean IQ of survivors, this was at the expense of a selection process whereby increased numbers of abortions, stillbirths and neonatal and childhood deaths killed all but the most resilient and best-fed children. Unlike these unique conditions during World War II, chronic protein deficiency, which is called kwashiorkor in medical jargon, continues unabated in many areas including Uganda and Jamaica, where it has been linked to shortened stature and blunted intelligence.[9,10] Lending these considerations added urgency are two recent reports in *Lancet*[11,12] suggesting that at least short-term kwashiorkor-induced mental deficiency may be reversible with improved nutrition.

Clearly, the health profession is in need of some very careful distinctions in this regard. Of course everybody regrets the conditions detailed above, but the plain fact is that they lie completely outside the realm of medicine. Food distribution is the province of economics and politics. If the United States government chooses to spend 55,000 lives and $400 billion on a military venture in southeast Asia rather than attempt to eradicate malnutrition, we in our hermetic medical fortress are insulated against all recriminations. Let the government consult us in our laboratories on the consequences of malnutrition or let the undernourished visit our clinics and we will respond with the technical perfection which is the hallmark of American medicine; but heaven forbid that we should forsake the carefully drawn distinctions which guard the ramparts of our optimal world to respond to suffering and disease due to nonmedical factors.

Regrettably, certain misguided detractors make this careful attention to qualifications and provisos as needful domestically as abroad. R. M. Factor and Ingrid Waldron[13] have shown a positive correlation between mental hospital admission rates and four factors in Cook County, Illinois: population density, high concentration of multiple-dwelling units, frequency of dwelling changes and low percentage of home ownership (that is, the four factors which functionally define a ghetto).

On another front, J. P. Bunker and J. E. Wernburg[14] have recently focused on the relationship between surgical operations and health. Canadian gall bladder operation rates are five times those in the United Kingdom, and mortality from gall bladder inflammation is twice as high in Canada as in the United Kingdom. Unless cholecystitis is far more aggressive in North America than in Europe, an unlikely possibility, one must attribute these differences primarily to surgical aggressiveness. Similarly, a county-by-county analysis of operation rates and mortality in Vermont showed a positive correlation between the two, a fact which must be attributed either to differing rates of surgical disease, which seems unlikely, or to unfortunate variations in surgical judgment. Finally, Duncan Neuhauser at the Harvard School of Public Health has estimated that operative mortality for inguinal hernia is about four times

the nonoperative mortality in the population over sixty-five, and yet the number of elective herniorrhaphies in the Medicare population has doubled since 1965. And while the nature of surgical therapy makes statistical compilation and comparison easier than for medical treatment, there is little doubt that similar comparisons could be made among medical specialties.

These observations all seem unsettling unless the proper distinctions are drawn. The prattle about living conditions and mental health is attributable to domestic social policy and economics, as far from the idyllic domain of medicine as worldwide malnutrition. As for that petty cavilling about potentially adverse effects of medical or surgical therapy, a chorus of qualifications clamors to be heard. Only by maintaining great medical fortresses can sufficient rigors and adequate competition be insured during the training process to generate a hierarchy appropriate for the best of all possible medical worlds. If this fosters a crisis-intervention concept of medical practice rather than health maintenance, then this is necessarily for the best. If the responsibilities of a training physician teach him to pare to a minimum the time spent with each patient, then this lesson will be carried into his practice where the most rapid and profitable diagnosis and therapy possible will be effected, as is proper in this optimal of all possible medical systems. Therefore it can be seen that as long as we continue to carefully defend our boundaries, we are about to enter the best of all possible professions.

In light of the foregoing remarks and in the context of current medical controversy, it is obvious that our vigilance must be increased and our logical scalpels ground exquisitely sharp if we are to preserve this medical fortress nonpariel against the erosions of a responsibility for or response to pandemic malnutrition, diseases of sociopolitical origin or painful and unprofitable criticism. So it is even at this joyous time incumbent on me to reprimand my classmates and many if not most of our otherwise superb faculty—for they have failed to make these proper distinctions, many times consistently and even intentionally. Indeed this influence has been so pervasive at this school that I myself find the logic which defines this best of all possible medical professions progressively less accessible. During these ever more frequent spells of weakness induced in me by this school's distinction-blurring miasma, dimly I have begun to see a vision. It is a finite and even fallible world bereft of fortresses and speck-like pilgrims living in abstract murals, with doctors who are blind to the speciation of suffering, but not to its causes or its cures. Indeed, it is a world so far from being perfect that it is merely human.

REFERENCES

1. Voltaire: Candide. New York, Signet, 1968, p 17
2. Cook RW: Nutrition and mortality in the Caribbean population less than five years old. J Trop Peds 15:109-117, Sep 1969
3. Cabac V, Najdanvic R: Effect of undernutrition in early life on physical and mental development. Arch Dis Child 40:532-534, 1965
4. Stoch MB, Smythe PM: The effect of undernutrition during childhood on subsequent brain growth and intellectual development. South African Med J 41:1027-1030, Oct 1967
5. Pollitt E, Granoff D: Mental and motor development of Peruvian children treated for severe malnutrition. Rev Interamer de Psicol 1:93-99, 1967
6. Chase HP, Martin HP: Undernutrition and child development. N Engl J Med 282:933-939, Apr 1970
7. Champakam SG, Srikantia SG, Gopalan C: Kwashiorkor and mental development. Am J Clin Nutr 21:844-852, Aug 1968
8. Begab MJ: The major dilemma of mental retardation: Shall we prevent it? Am J Ment Defic 78:519-529, Mar 1974
9. Hoorweg J, Stanfeld P: The influence of malnutrition on psychologic and neurologic development: Preliminary communication, *In:* Nutrition, the Nervous System and Behavior—Conference Proceedings, Panamerican Health Organization, 1972
10. Richardson SA, Birch HG, Grable E, et al: The behavior of children in school who were severely malnourished in the first two years of life. J Health Soc Behav 13:276-284, Sep 1972
11. Valman HB: Intelligence after malnutrition caused by neonatal resection of ileum. Lancet 1:425-427, Mar 1974
12. Lloyd-Still D, Schwachman H: Intelligence after malnutrition. Lancet 1:679, Apr 1974
13. Factor RM, Waldron I: Contemporary population densities and human health. Nature 243:381-384, Jun 1973
14. Bunker P, Wernburg JE: Operation rates, mortality statistics and quality of life. N Engl J Med 289:1249-1251, Dec 1973

Special Article

Refer to: Butler LM: Malpractice insurance—A crisis in medicine. West J Med 123:328-336, Oct 1975

Malpractice Insurance — *A Crisis in Medicine*

LEONA M. BUTLER, *San Francisco*

EDITOR'S NOTE: *The following is probably as good an account as there is, or is likely to be, of the San Francisco experience with the anesthesiologists' "walk out" in May of this year. It is adapted from an article that appeared in the Fall issue of* Spirit, *a publication of the Pacific Medical Center, issued for the friends, volunteers and staffs of that hospital. It is written with sympathy for physicians but brings home the prompt and very serious effects of a physicians' strike upon hospitals and hospital personnel as well as upon patients.*

—MSMW

THIS IS A REPORT on the medical malpractice crisis in San Francisco, a crisis in which Presbyterian Hospital of Pacific Medical Center (PMC) was critically affected. During the crisis, the employees of the hospital worked harder than ever, in fewer hours and for smaller pay checks, to successfully maintain high standards of patient care.

What Went Wrong?

Since 1968 when premiums for a general surgeon's professional liability, or malpractice, insurance jumped from $756 to $1,688 a year, there has been a growing concern among physicians, insurance companies, legislators and others about the rising cost of medical malpractice insurance. Despite continuing hearings, sporadic brainstorming sessions and lengthy investigations, particularly the Department of Health, Education, and Welfare's $2 million study published in 1972 by its Special Commission on Medical Malpractice, the issue failed to be resolved, until, by December 1974, it appeared that a crisis of far greater proportions than ever imagined would soon be at hand.

The author is Director of Public Relations at Pacific Medical Center, San Francisco.

Reprint requests to: Leona M. Butler, Director of Public Relations, Pacific Medical Center, P.O. Box 7999, San Francisco, CA 94120.

In late 1974 hospitals, too, were facing rate increases of an average 75 percent for their institutions' malpractice insurance. At Presbyterian annual premium rates jumped from $196,000 to over $450,000.

Complex reasons for the impending crisis began to emerge—reasons which pointed to problems far deeper than administration of insurance:

Increase in the size of awards made against physicians and hospitals. In 1974, for example, there were 32 malpractice awards of more than $300,000 compared with three such awards in 1969. Of the 1974 awards, 17 amounted to more than $1 million with one settlement of $4.25 million.

Increase in the number of claims filed as malpractice suits. Where such claims had once been uncommon, as *Newsweek* reported: "More than 20,000 malpractice claims are now brought against doctors each year and the number is rising steadily." Approximately 45 percent of the country's malpractice suits are dismissed as frivolous and a mere three percent of those tried in court are actually won by the plaintiffs. While the dollar amount of malpractice judgments had quadrupled between 1969 and 1974, the actual number of verdicts had been reduced.

Growth of consumerist-oriented society which

demands compensation for any injury, ranging from the purchase of a faulty toaster to the results of sophisticated surgical procedures. As a California insurance representative put it, "People now want to be compensated even if an honest mistake has been made, not only when there has been demonstrable negligence."

Decrease in long-term physician/patient relationships. In a mobile society, particularly in urban areas, these relationships of mutual trust do not have the opportunity to develop and an increased tendency to sue is one consequence.

No definable limit on the statute of limitations in medical malpractice. According to insurance company testimony, "Many of our cases are still active as much as five to ten years after expiration of the policy."

Increase in the amount of coverage required for the protection of patients and physicians. Whereas in 1966 a physician needed between $100,000 and $300,000 in malpractice coverage, by 1974 his insurance needs ranged from $1 million to $3 million. Premiums for such policies naturally rose: the general surgeon who paid $1,688 in 1968 for his insurance paid over $3,588 in 1974.

Inability to inform juries of a patient-plaintiff's collateral sources of income. Such income might include disability insurance and payment of medical costs by a group health plan. Furthermore, the jury is not permitted to know that its verdict is *not* subject to federal and state income taxes.

Loss of capital reserves by major malpractice insurance companies. High jury awards and a severe drop in the stock market had left many companies desperately short of reserves necessary to write malpractice insurance. While dozens of companies had once provided this coverage, by January 1975, there were five. Major insurance companies throughout the country were indicating they could no longer afford to write malpractice insurance.

How Did It Happen?

Late in 1974 the stage was set for action. One of the largest companies still providing malpractice insurance was the Argonaut Insurance Company of Palo Alto. It too was in serious financial difficulty by the end of 1974. The company's group policy held by 4,000 physicians in San Francisco and seven other Northern California counties was up for renewal on May 1. With Argonaut discontinuing its coverage of physicians elsewhere in the country, the fear arose that physicians were facing a possible loss of available insurance.

In mid-December State Insurance Commissioner Gleason L. Payne—in an attempt to keep physicians in practice—called upon California Governor Edmund G. Brown, Jr., to create a "no-fault" malpractice pool among the state's 1,000 casualty indemnity companies.

Commissioner Payne also proposed laws to take most malpractice cases out of the courtroom, pointing out that under the present system, which provides for lawyer contingency fees, some $40 million goes annually to the attorneys trying malpractice cases. Noting that the patient-plaintiff often receives less than one-third of the larger court settlements since most of the money is absorbed by the judicial process, Payne recommended a sliding scale for attorney fees which would remove the incentive for reaching such huge settlements.

The possibility of federal intervention arose. According to Roger O. Egeberg, MD, Special Assistant to HEW Secretary Caspar Weinberger, the malpractice insurance problem had cost the government nearly $6 billion in 1974. Of that amount between $1 billion and $2 billion was paid in bills which reflected the rising cost of insurance to hospitals and physicians. The balance of $4 billion was paid, Dr. Egeberg reported, "because the continual threat of suit has caused physicians to practice 'defensive' medicine to protect themselves against malpractice allegations."

According to Dr. Egeberg, one of the saddest aspects of the situation is that only 17 cents of every malpractice insurance dollar ever gets paid to an injured patient. The other 83 cents goes to prosecuting and defending attorneys, investigation costs, witness fees, salesmen's commissions and insurance company costs.

The government today is the nation's biggest payer of medical bills. Fifty million Americans have part of their health care costs paid from Medicare, Medicaid (in California, Medi-Cal) and maternal and child health programs.

Insurance Policies Cancelled for Northern California Physicians

As feared, on January 31 physicians were notified that, effective May 1, Argonaut would cancel the group plan it held with the San Francisco Medical Society and seven other Northern California counties. Spokesmen for Argonaut indicated individual insurance would be available for

certain physicians who qualified. But for those who did qualify premiums would be increased as much as 384 percent.

It appeared that many San Francisco doctors would not be able to buy insurance by May 1 and those who could faced enormous rate increases which would ultimately be passed on to patients. Physicians already were charging 15 percent of their patient bills to the costs of malpractice insurance and were reluctant to increase this amount.

Once again, State Insurance Commissioner Payne warned Governor Brown that without a solution a major health care crisis could occur. Indeed, many physicians had begun seriously to consider shutting down their offices, while younger doctors indicated they could be forced either to quit the profession, become employees of prepaid health care plans such as Kaiser Permanente, or move to another state. Daily, there were accounts of older doctors deciding on early retirement rather than attempt to pay the insurance increases.

By late March, although a number of malpractice bills had been introduced, none of the proposed legislation would affect insurance rates. No immediate solution was in sight. It was clear that legislation which could solve the intricacies of the imminent crisis would take far longer to enact than the rapidly approaching May 1 Argonaut deadline. Doctors, particularly anesthesiologists, started to talk of discontinuing services.

Hospitals, meanwhile, were informed by their carrier, Farmers Insurance Company, that any hospital which allowed a physician to practice without malpractice insurance coverage would lose its own malpractice insurance. The risk to a hospital would be too great: lawsuits brought against an uncovered physician would become the responsibility of the hospital where the incident occurred.

By March 31, statements signed by staff physicians began to appear on hospital bulletin boards saying the doctors would be unable to afford insurance under announced rates. Many doctors informed hospitals—and patients—that they would be forced to suspend practice as of May 1 unless a reasonable solution were found. Emergency plans were designed for patients to be directed to one of the city's six public hospitals, where staff physicians are considered employees and therefore covered by the hospital's own insurance. (Ironically, these hospitals were not unaffected by the crisis: for example, insurance for the University of California hospitals jumped in early 1975 from $4,000,000 to $10,000,000.)

A month from the May cancellation date, Argonaut, which in January had agreed to grant temporary coverage to some physicians, now mailed notices to *all* physicians covered under its group plan offering them coverage at rates three to four times higher than 1974 rates.

Physicians are charged varying rates for insurance depending on their medical specialty. Anesthesiologists, orthopedic surgeons, neurosurgeons and others in the high risk groups now received bills of over $18,000 for a year's malpractice coverage. For the year ending April 30, 1975, they had paid $5,377.

The question shifted from whether insurance would be available to whether all doctors could afford such insurance, and attention was focused on physicians in the high risk specialties.

Solutions to Crisis Sought in Sacramento as Doctors Threaten Walk-out

Alarmed that no solution was in sight, PMC administration had joined physicians in urging hospital trustees, employees, patients and support groups to write the Governor and state legislators for enactment of short- and long-term solutions. Interestingly, it was not until these letters and telegrams from the public started to arrive that the majority of northern California Assemblymen and Senators began to express their concerns about the crisis.

Meanwhile, the San Francisco Medical Society worked at establishing their own insurance company; individual physicians and several county medical societies brought suit against Argonaut for breach of contract; legislators attempted a bill that would temporarily freeze insurance rates at 1975 levels, and the California Hospital Association attempted to get the Governor or State Insurance Commissioner to use emergency powers to hold back rates.

Bay Area anesthesiologists began meeting together in mid-April as an ad hoc committee to consider available options. Faced with the most significant increases, they were outraged at the lack of solutions forthcoming from Sacramento. The possibility of the majority of San Francisco anesthesiologists "going on vacation" became very real.

There are approximately 70 anesthesiologists

in San Francisco. Most surgical operations cannot be carried out without one of them.

In April, San Francisco hospital administrators, among them PMC president Clifford F. Schwarberg, Jr., had begun the first of many trips to Sacramento to meet with legislators, Governor Brown, the insurance commissioner and other state officials. Their purpose was to alert those who could influence the Legislature to the jeopardy in which hospitals were being placed and to assist them in the formulation of realistic and workable solutions.

In addition to Schwarberg, the San Francisco Hospital Conference's ad hoc Committee on Malpractice included Jay Okun Yedvab, executive director, Mount Zion Hospital and Medical Center; Joseph L. Zem, administrator, Saint Luke's Hospital; Robert Densmore, administrator, Children's Hospital of San Francisco; and A. Dale Morgan, administrator, Marshall Hale Medical Center. These men represented the hospitals which were to be the most affected by an anesthesiologist work stoppage. These are the major community hospitals in San Francisco which conduct the majority of health-sciences teaching programs, free and partial pay clinics, medical research and on-going community programs. They consequently bear the largest cost burdens, employ the most people, and have the heaviest commitments to patients, students and the public.

A legislative package encompassing needed reform was introduced on April 18 by Assemblyman Howard L. Berman, chairman of the Assembly Select Committee on Medical Malpractice. However, in no way could these bills be enacted by May 1.

Hospitals Gear Up for Walk-out

In mid-April PMC announced to employees that preparations were being made for the eventuality that on May 1 a significant number of physicians would choose not to practice under the severe rate increases.

Presbyterian Hospital is a 311-bed acute care hospital (exclusive of psychiatry which is located in a separate building). The administration estimated that if routine surgical operations could not be done, there would be a reduction of patient census to an average of between 120 and 140 patients. (This proved to be an extremely accurate forecast.) Work force would, of course, have to experience an equivalent reduction.

Before and throughout the crisis, employees were kept as informed as possible of contingency plans and of possible lay-offs. In mid-April, where possible, employees were given, on a unit by unit or department by department basis, the opportunity to have a voice in how potential work-force reductions would be handled. All possible alternatives to actual lay-offs (such as reduction in work weeks, early vacations and the like) were developed for personnel.

On April 27, Presbyterian and all other San Francisco nonprofit community hospitals were informed by their anesthesiologists that most of them would no longer carry insurance as of May 1, and would therefore be unable to practice. Presbyterian was told that one anesthesiologist, who had already purchased individual insurance, would be available on-call for emergency surgical procedures only. Any urgent cases, or those cases which could be transported without serious risk, must be sent to one of the public or federal hospitals.

Since Presbyterian Hospital is a highly-specialized acute care hospital, approximately 56 percent of its admissions are surgical patients. A large percentage of these patients come from beyond the Bay Area for such specialized surgical care as open heart surgery, total hip replacement, neurosurgery, eye surgery and various types of microsurgery. Some of the surgical cases planned for May could be temporarily postponed without undue risk. Others could not.

By April 26, all surgical operations scheduled at PMC for May had either been postponed or referred to an unaffected hospital. And, at approximately 2 p.m., April 30, what was to be the last scheduled operation for over a month began at PMC. No doctor would undertake a surgical procedure later in that day for fear it might last beyond the midnight deadline.

Presbyterian Hospital was about to lose more than half of its patients.

The Walk-out Begins

May 1 the patient census at PMC dropped drastically. For nearly a week before the deadline doctors had not admitted any patients who might need surgical operation, even if they were being admitted for medical purposes only. In spite of the precaution the first patient to be transferred for an operation was moved to the University of California Hospital shortly after midnight on May 1. An average of five patients daily were to be transferred from PMC during May.

Guidelines for moving patients were immediately put into effect. No patient was to be transferred without authorization by the president of Pacific Medical Center. The patient's physician must state that in his opinion the patient's condition would in no way be aggravated by the move. There must be assurance that the patient had been authorized for acceptance by a physician at another hospital.

If a patient needed an operation and could not be moved from Presbyterian without danger, his physician would present the case to the department head of the surgical service involved and the on-call anesthesiologist.

Each morning throughout the walk-out, a PMC management team met to discuss that day's projected census, staffing levels, purchasing plans, legislative action, employee morale and the overall effects which the crisis was having upon the hospital. Of greatest concern to this group was the need to carry on quality health care in spite of all necessary cutbacks.

And cutbacks were necessary since PMC's income, it was apparent, would be cut more than half by the walk-out. Even if personnel and purchasing costs could be cut by that amount, fixed costs, such as hospital insurance, maintenance of buildings and equipment, income and principal on the building and security, would remain unchanged. Such fixed costs represent approximately 40 percent of PMC's $29 million annual budget.

Anxious to avoid lay-offs of personnel, PMC explored other means of cutting the work force. Most personnel were cut to three and four day weeks, and early vacations were offered where possible. Leaves of absence were encouraged. All purchasing was halted except for those supplies needed on a day-to-day basis. Administrative salaries were cut by 20 percent with some taking even larger cuts. Interns and residents voted to accept one day a week less salary.

Meanwhile, by the first weekend in May it appeared that with the exception of anesthesiologists and some surgeons, most physicians, particularly internists and others in low risk categories, had obtained insurance for at least three months.

The immediate effect of the walk-out, then, was to be almost entirely in the area of surgery.

The public, however, did not yet know this and the first weekend in May a curious phenomenon occurred. Emergency rooms throughout the city, including those in unaffected hospitals, had what may have been the quietest weekend ever experienced. Unaccountably people did not seem to get sick. Oddly, the decrease in activity was not only among persons with minor ailments. Emergency rooms experienced the same cross-section of illnesses and injuries as usual—only fewer of them. Perhaps, being unsure of the availability of care, people stayed well.

By Tuesday, May 9, the census at Presbyterian had dropped to 166. There had been a 20 percent reduction in work force and a loss of nearly $19,000 per day. The equivalent of an entire nursing floor—six 18-bed units—had been shut down.

Physicians Go to Sacramento

Under the state's constitution the Governor can call a special session of the Legislature to run concurrently with the regular session in order to consider and act upon a specific problem. Bills enacted in a special session become effective immediately if an urgency clause is attached or, without such a clause, within 91 days after the session adjourns. Bills enacted in a regular session normally do not become law until January 1 of the following year. A bill can be enacted as urgency legislation without a special session and becomes law in 31 days after passage; however, this requires two-thirds majority vote—something extremely difficult in such intricate issues as malpractice reform.

Physicians had determined that a special session of the Legislature could help achieve their purposes, and on May 9 anesthesiologists and hundreds of other physicians met in Sacramento where they urged Governor Brown to help obtain speedy legislative relief by calling a special session on malpractice. By that time most physicians had become angry and disappointed that of the 22 bills introduced thus far only one had reached the Governor's desk.

The Sacramento meeting revealed a deepening gulf between physicians and legislators. Speaker of the Assembly, Leo T. McCarthy, a Democrat from San Francisco and key leader in getting votes, was one of several legislators who told the doctors to go back to work. At one point he said legislative action would take "at least several months." In the interim, McCarthy said, doctors would have to pay the drastically higher premiums so they could care for their patients. That satisfied no one in his audience.

The Walk-out Spreads to Other Parts of State

In mid-May, San Francisco anesthesiologists traveled throughout California providing information and enlisting the support of others. There was now increasing news of potential disruption of surgery schedules in most sections of California. Physicians had been spurred on by the news that the Travelers Corporation, a major malpractice insurer in other areas of California, intended to raise malpractice rates a staggering 400 to 600 percent.

On May 8, anesthesiologists in Santa Clara announced that they would join their colleagues in San Francisco, Marin, Alameda and Contra Costa Counties by administering anesthesia only in life-or-death situations.

In deep concern, the San Francisco Hospital Conference called a news conference on May 8 to urge the Governor to call a special legislative session and to call upon physicians to return to practice if such a session were announced.

Speaking for the Hospital Conference, A. Dale Morgan reported a work force reduction of 3,000 employees from a total of 8,500 and an economic loss of about $200,000 per day.

At Presbyterian everything not essential to patient care had been eliminated. The Café, outpatient pharmacy and cafeteria grill were closed; publications had been suspended; no coffee or meals were served at meetings; minimal cleaning was done in nonpatient areas; personnel was not available to run audiovisual equipment for educational programs; there were no tours, no Auxiliary events.

Employees March on Sacramento

Employees, working harder for less pay, had maintained an excellent morale. But they were becoming frustrated. They saw their jobs dissolving and their hospital in serious financial jeopardy. There seemed to be nothing they could do about it for themselves.

Friday, May 9, employees asked the PMC administration for help. They wanted to go to Sacramento and talk directly to Governor Brown and the legislators about what the crisis was doing to San Francisco and to their jobs. PMC president Schwarberg promised employees if they could organize it, he would provide assistance.

Within two hours all departments were notified. Approximately 75 people arrived for a 5 p.m. meeting to plan the trip to the state capitol.

Off-duty employees would go to Sacramento the following Tuesday and invite the employees of the other San Francisco hospitals to go with them. Auxiliary president Nancy Caton got approval for Auxiliary funds to pay for bus rental. Committees were formed for bus monitoring, sign and placard making, telephoning, providing liaison with other hospitals and writing informational materials and petitions.

On Tuesday, May 13, over 800 hospital employees from Presbyterian, Mount Zion, St. Luke's, Children's and St. Francis Hospitals arrived at the state capitol bearing signs reading, "Save Your Hospitals—Save Our Jobs," "Our Hospitals Are in Cardiac Arrest," "The Life We Save May Be Yours" and "Special Session Now." Nurses, lab technicians, dishwashers and personnel representing most hospital related occupations were there to listen and be heard.

Spokespersons had been elected for each hospital. At a rally on the capitol steps they talked about the hospitals they represented. They pointed out that their hospitals admit 60,000 inpatients each year, half of the nonfederal hospital admissions in San Francisco. Their hospitals, they explained, have 355,000 clinic visits annually, employ 5,500 people and train 12,000 persons each year in medicine, dentistry, psychiatry and other health professions, including minority upgrading programs. They reported if something were not done to solve the crisis, their hospitals would have to consider closing by Memorial Day.

On the capitol steps, San Francisco Senators and Assemblymen met with the unemployed employees. The lawmakers were sympathetic about the hospitals, but not about the plight of the doctors. Almost without exception, legislators said, "Tell the doctors to go back to work." And each time a resounding "No" was the response. Employees wanted their jobs but they also wanted the crisis solved.

Assembly Speaker McCarthy told the group it would be months before remedial legislation could be passed into law. During a spirited exchange with protesting employees, he admitted, "This is an absurd kind of dilemma that we've allowed ourselves to drift into." He finally promised employees, who would not accept having the blame laid at the feet of the doctors, "Something will be done before the end of the week."

Every lawmaker to whom the employees spoke reported it was the Governor alone who could call

a special session—it was out of their hands. Some promised to contact the Governor to push for the session.

Employee spokesmen waited in the Governor's reception room and vowed not to leave until he talked to them. They sent into his office several large petitions calling for the special session.

First the Governor sent out his press secretary to talk to them. Then he sent Health and Welfare Secretary Mario Obledo to talk to a quickly assembled group of 150 employees. But when Obledo could not satisfy the employees, who felt that the one person in the state who could do something was the one person who refused to see them, he got the Governor.

After hearing from employees, Governor Brown told them he would call a special session when he got agreement on an agenda which would include not only malpractice reform but also a series of measures to further regulate the health care delivery system in California. He felt San Francisco had too many hospital beds and wanted to look into that; he wanted to further regulate hospital rate setting; he wanted to look into the basis on which students were admitted to medical school.

As McCarthy had told employees, "Before this is all over we're going to take a bite out of three parties; the insurance industry, the attorneys and the physicians." Brown had added a fourth—the hospitals.

On May 16, the Governor issued a proclamation calling the session. The employees' action at the state capitol was certainly one of the major factors influencing the Governor's action. For the first time in the crisis he had heard directly from the people.

In announcing the special session, Brown said, "The inability of doctors to obtain insurance at reasonable rates is endangering the health of the people of this state and threatens the closing of many hospitals. The longer term consequences of such closings could seriously limit the health care provided to hundreds of thousands of our citizens."

The Governor's program for a special session on malpractice included:

1. Reconstituting the Board of Medical Examiners to include a majority of public members;
2. Giving the board full authority to discipline and decertify practitioners for lack of competency;
3. Providing the board with authority to set recertification standards including updated training and public service, in order to minimize malpractice and increase the quality of medical care;
4. Providing the board with authority to minimize the present maldistribution of medical care in certain areas of the state;
5. Establishing a Medical Peace Corps to service Californians who lack adequate medical care;
6. Regulation of hospital rates, including authority over excessive hospital bed capacity and unnecessary duplication of expensive and underutilized equipment;
7. Voluntary binding arbitration in order to quickly and fairly resolve malpractice claims while maintaining fair access to the courts;
8. Establishment of reasonable limits on the amount of contingency fees charged by attorneys;
9. Elimination of double payments (collateral sources); institution of periodic payments and reversionary trusts; limitation of compensation for pain and suffering while insuring fully adequate compensation for all medical costs and loss of earnings; and setting new reasonable statute of limitations for the filing of malpractice claims.

In addition Governor Brown stated he would: (a) Convene a Special Panel to immediately conduct a complete investigation into all insurance company rates and reserve practices; and (b) support legislation in the regular session to insure adequate public representation on all professional boards, including the Board of Governors of the California State Bar.

Indeed, it appeared that this special session would not deal solely with the medical malpractice issue. As one national television commentator remarked about the situation: "The Legislature is studying a complete reform of health care delivery in the state of California."

Walk-out Continues to Have Impact on Hospitals

While the trip to Sacramento was being planned by hospital employees, the PMC patient census had dropped down to 106. Eight nursing stations, the coronary care unit and the intensive care unit were now closed. An estimated $35,000 a day was lost one weekend alone.

In addition to the effects on employees and on special programs, the crisis had begun to take its toll on teaching programs for young doctors. Without surgical operations, surgical residents had little to do and were gaining little experience.

Doctors began looking for things for interns and residents to do.

In going into the crisis the hospital financial picture in San Francisco was far from healthy. Many of the hospitals had experienced a six-week nurses' strike less than one year before and had not yet recovered from its effects. With one exception the city's hospitals already had huge loans for remodeling and construction of replacement facilities. Drastically rising costs of personnel, supplies, food, malpractice insurance, along with the inability of hospitals to pass these increases on to Medicare and Medi-Cal patients, had all contributed to the hospitals' financial problems. Added to this was the cost of teaching programs, free and partial pay clinics and other community service programs borne by the major teaching hospitals which, unlike the University of California Hospitals, are not funded by the state.

At PMC, however, cutbacks had been achieved to the point that the Board of Trustees task force on malpractice, which had been investigating the hospital's financial viability, concluded that Presbyterian Hospital could continue to survive while meeting its financial obligations.

Confusion Continues as Physicians Announce Plans to Return to Work

Hopes had run high that once Governor Brown called a special session—a so-called "act of good faith"—the anesthesiologists would return to work and allow the Legislature to work on reform measures.

People began to realize the special session was far from being a cure-all. While bills passed under this aegis could become effective immediately, there was no guarantee the needed bills would, in fact, be passed. Bills already introduced and on their way through committee would have to be dropped and reintroduced to come under the time advantages of the special session. However, there was no certainty that anything would go through a special session faster than in an ordinary session.

Meanwhile the anesthesiologists in Southern California who had not yet lost their insurance had begun, hospital by hospital, to discontinue services in support of the San Francisco physicians. It seemed that anesthesiologist leaders who had been traveling through California to enlist support were finally realizing results. Consequently more anesthesiologists than just the San Francisco group were becoming involved in decision making. An organization had been started. Emotions were running high. How could the protest be stopped once it was truly under way?

San Francisco anesthesiologists felt they could not return to work now that they were getting others out in their support. The fact that San Francisco hospitals had already suffered through three weeks of drastically lowered census was not a factor they could take into account. As one newspaper said, "The malpractice mess gets even messier."

It was Memorial Day weekend. At Presbyterian Hospital a patient had been admitted a week and one-half earlier in severe pulmonary edema. He had been rushed to the hospital from Eureka, over 300 miles north of San Francisco, referred by his physician to doctors at Presbyterian where sophisticated knowledge and equipment would, it was hoped, save his life. He had almost lost the function of his only kidney.

Placing him in the hospital's cardiopulmonary intensive care unit and getting him on kidney dialysis, doctors pulled him through the initial crisis. Extensive tests were made and it was discovered that the patient, 58-year-old Rexford Tieg, had a severe blockage of an artery leading to his kidney—to the extent that it had already lost 90 percent of its function. Delicate vascular surgical procedures were needed to save the kidney and prevent Tieg from spending the rest of his life on kidney dialysis, three days a week, four hours a day.

Tieg was scheduled for surgery. The chief of anesthesiology, however, refused to allow anesthetic. Tief's operation was, indeed, urgent and his condition life-threatening. However, his condition had improved to the point that he could be considered transportable. Tieg's physician, his surgeon and even PMC's president spent the weekend negotiating with the chief of anesthesiology, trying to get agreement for the operation at Presbyterian. Although he was "transportable," the operation would require him to be at a hospital which had heart-lung and dialysis equipment. (Tieg was already the victim of three heart attacks.) He would require a highly specialized cardiovascular surgeon. This eliminated most of the nonaffected hospitals.

In desperation, Mrs. Tieg, herself a registered nurse and very knowledgeable about her husband's condition, called the news media. Tieg's story was publicized locally and nationally.

The unaffected hospitals in the San Francisco

area equipped to handle Tieg's operation were full to overflowing by this time and could not guarantee they would be able to schedule it in time to save his only kidney.

Finally, on Tuesday, May 27, El Camino Hospital, over 30 miles from San Francisco and also one of the hospitals affected by the anesthesiologists' walkout, got agreement from their anesthesiologist to do the operation. It was done the following day at El Camino Hospital and, as of this writing, he is recovering well and has regained the use of his kidney.

The PMC Medical Staff had an emergency meeting the night of Tuesday, May 27. News stories of the Tiegs had an effect. For the first time, physicians realized the situation was causing a real deterioration in patient care. Representative anesthesiologists were present from all San Francisco and Marin hospitals. It was the first time they heard a call from fellow physicians to return to work.

On Wednesday, May 28, the San Francisco *Examiner* headlined: "Doctors End Their Protest —Agree to Return to Work."

It happened in great confusion.

Anesthesiologists meeting that morning agreed they would have to get back to work. An afternoon meeting was scheduled in Sacramento with Speaker McCarthy, hospital administrators and other concerned representatives.

A few days before this meeting, Assembly Bill 491—the Behr Bill—had been passed and signed into law allowing the State Insurance Commissioner to form a joint underwriting insurance pool composed of all casualty and liability insurance companies in the state. The pool would provide a "claims made" policy at 1974 rates until January 1976, at which time the policy would be convertible to an "occurrence" policy.

A "claims made" policy is one which provides insurance for claims made during the year of coverage. Under current statute of limitations on malpractice, doctors would have to continue to carry such insurance indefinitely for claims incurred in one year, which are not made until as much as 20 years later. An "occurrence" policy covers a physician for claims made at any time if the physician carried the insurance the year the injury took place.

Before the McCarthy meeting, anesthesiologists started telling reporters they would be reporting to work.

Insiders were confused. The Behr Bill, under which the anesthesiologists said they were returning, had been previously rejected soundly by most physicians. It was feared that the bill could create even higher premiums than the 1975 rates.

Now, however, anesthesiologists were saying that they had reached their short-term objectives and would return to work while the Legislature worked on long-term reform.

PMC president Schwarberg, who was in Sacramento with the anesthesiologists, was understandably skeptical. He was assured by Laurens Garlington, MD, leader of the group and chief of anesthesiology at PMC, that the hospital could schedule operations for the following Monday. Anesthesiologists would guarantee to be there even if something went wrong; they would work as volunteers.

Something did go wrong—the following day.

Anesthesiologists suddenly realized the "claims made" policy they were accepting would carry with it a potentially huge "tail payment" possibly for years to come. They felt doublecrossed by the Legislature. It was an extraordinary situation—apparently, in accepting the Behr Bill, the anesthesiologists had not read it thoroughly.

Hospitals were in turmoil. Were they or were they not going back? Morale sank to a new low. Realizing the chaos they had created, anesthesiologists knew they must now return to work, and decided there was no alternative but to purchase individual insurance at 1975 rates for a three-month period. Thus, the joint underwriting insurance bill was not activated by the insurance commissioner.

The Doctors Return to Work

During the week of June 2, the doctors straggled back to work as individually they obtained their malpractice insurance. Hospitals, unable to get firm estimates of how many, and when, anesthesiologists would return, were little better off in their efforts to schedule surgical operations than they were during the strike. This tenuous situation existed into the second week of June.

When the news came that the doctors were returning, there could, in fact, be little rejoicing in hospitals where the news came too late, conditions were too grim, too many people had been laid off and too much money lost. It would not be "business as usual" in San Francisco hospitals for some time to come.

Refer to: Richardson RG, Parker RG: Metastases from undetected primary cancers—Clinical experience at a radiation oncology center (Medical Information). West J Med 123:337-339, Oct 1975

Metastases from Undetected Primary Cancers

Clinical Experience at a Radiation Oncology Center

R. GARRATT RICHARDSON, MD
ROBERT G. PARKER, MD
Seattle

MANAGEMENT OF PATIENTS with initial symptoms or signs produced by metastases may be difficult but rewarding. The clinical entity in which the presenting findings are related to the distant spread of cancer has been termed "precocious metastasis."[1] There is a subgroup of these patients in whom, despite thorough investigation, no primary tumor site can be identified. These patients often are referred for radiation therapy of their symptomatic metastases. The natural history of a group of these patients has been reviewed.

Materials and Methods

Between 1960 and 1973, 86 patients were referred to the Division of Radiation Oncology at the University of Washington with the diagnosis of metastatic cancer of unknown origin. This was a highly selected group of patients, in that only those patients thought to have metastatic disease which could be palliated by radiation therapy were referred. Thus, patients with liver and lung metastases generally were excluded. The primary site had not been established by the usual investigative procedures. Although most of these patients were older than 50 years, 10 percent were under the age of 40 (Figure 1). There were 63 males and 23 females. Eighty patients were white, three were black and one each was of Chinese, Hawaiian and North American Indian origin.

Bone was the most frequent metastatic site (38 percent) followed by nodes above the clavicle (28 percent), soft tissue (13 percent), brain (13 percent), mediastinum, infraclavicular nodes and lung (Table 1). Examples of soft tissue sites were pelvis, flank, leg, back of neck, umbilicus, buttock, orbit and scalp. The lung lesion was considered metastatic because of an elevated level of serum chorionic gonadotropin.

The biopsy specimens of all the lesions were reviewed by pathologists in the University of Washington teaching hospitals. In seven patients, there was not a histopathologic diagnosis before therapy. In two of these patients, cancer was confirmed at autopsy.

The distribution of histopathologic types in the metastases was undifferentiated malignant tumor —44 patients; adenocarcinoma—23 patients;

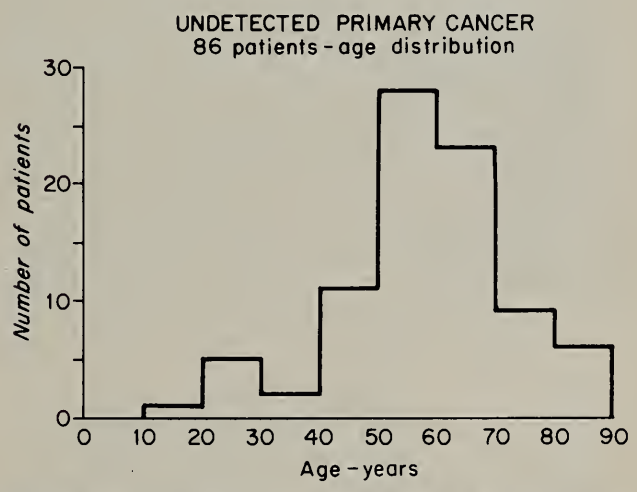


Figure 1.—Age distribution of 86 patients with undetected primary cancer.

TABLE 1.—*Sites of Metastases from Undetected Primary Cancer*

	Number	*Percent*
Bone	33	38.0
Lymph nodes		
above cavicle	24	28.0
below clavicle	3	3.5
Soft tissue	11	13.0
Brain	11	13.0
Mediastinum	3	3.5
Lung	1	1.0
TOTAL	86	100.0

Dr. Richardson is currently with the Virginia Mason Medical Center, Section of Radiation Oncology, Seattle.

Reprint requests to: Robert G. Parker, MD, Division of Radiation Oncology, NN146, University Hospital, 1959 NE Pacific Avenue, Seattle, WA 98195.

squamous cell carcinoma—11 patients (Table 2). The large proportion (50 percent) of the malignancies were undifferentiated cancers, reflecting the difficulty in determining the site of origin.

Treatment

Most patients received palliative radiation therapy to their symptomatic metastatic lesions. In a few patients with cervical node metastases, large tissue volumes including possible primary tumor sites, were treated to high doses with curative intent. The management of cancer in cervical lymph nodes in patients with an unknown primary site has been discussed by a number of authors[2-5] and will not be further elaborated upon here. Many patients who received palliative radiation therapy also received chemotherapy.

TABLE 2.—*Histopathology of Metastases from Undetected Primary Cancer in 86 Patients*

	Number of Patients
Adenocarcinoma (23 patients)	
Well differentiated	1
Moderately differentiated	5
Poorly differentiated	5
Differentiation not given	12
Squamous carcinoma (11 patients)	
Well differentiated	1
Moderately differentiated	3
Poorly differentiated	5
Differentiation not given	2
Undifferentiated (44 patients)	
Carcinoma	33
Sarcoma	1
Malignancy	10
Spindle cell malignant tumor	1
No histology	7

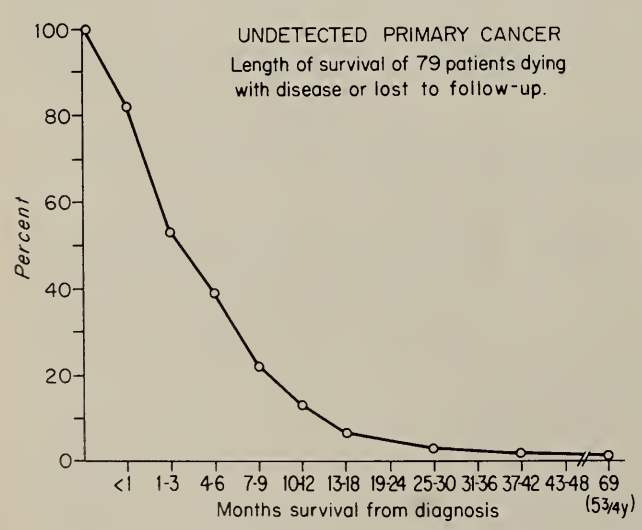


Figure 2.—Length of survival of 79 patients with undetected primary cancer who were dying with disease or lost to follow-up.

Results

In reviewing these data, two subjects were investigated: (1) the prognosis of the patient and (2) the subsequent identification of the primary cancer.

Prognosis

As expected, patients presenting with metastatic disease do not have a good prognosis (Figure 2). The nine patients lost to follow-up have been counted as dead after their last visit. Fifty percent of the patients died within three months of diagnosis and by one year only 12 percent of the patients remained alive. All patients who died had uncontrolled cancer. Some patients with undifferentiated cancers survived from two to five years, receiving additional palliative radiation therapy and chemotherapy. Seven patients were alive at the end of the study, having survived 7, 8, 9, 12, 24 and two for 46 months. Two of these patients had detectable tumor at 8 and 12 months while the other five patients had no evidence of

TABLE 3.—*Histology of Metastasis—Primary Site Subsequently Identified (22 Patients)*

Metastatic Site	*Primary Site*
Adenocarcinoma	
Ilium	Lung
Lumbar spine	Lung
Mediastinum	Lung
Thoracic spine	Prostate
Thoracic spine	Stomach (cytology)
Thoracic spine	Liver
Femur	Thyroid or lung
Squamous Cell Carcinoma	
Rt. supraclavicle	Lung
Mediastinum	Lung
Left neck	Lung
Right neck	Epidermal cyst of neck
Undifferentiated/Poorly Differentiated Malignant Tumors	
Thoracic spine	Lung
Thoracic spine	Lung
Lung	Lung
Groin soft tissue	Lymphoma
Ilium	Lymphoma
Brain	Lymphoma
Ilium	Kidney
Humerus	Kidney
Spine and pelvis	Pancreas
Soft tissue shoulder	Retroperitoneum
Brain	Hepatoma

TABLE 4.—*Metastases from Undetected Primary Cancers—Review of Literature*

Metastatic Presentation	Primary Identified/Number of Patients				
	38/233 ① Cervical Lymph Nodes	214/1,000 ② Supraclavicle Nodes—Infraclavicle Primary	9/42 ③ Axilla	42/162 ④ Adenocarcinoma 70 Percent with Liver Metastasis	22/86 ⑤ All Sites
Primary site					
Head and neck	11	..	1	..	..
Lung	11	67	1	1	9
Esophagus	2	5	..	..	..
Stomach and colon	4	32	2	10	1
Pancreas	2	9	..	16	1
Breast	1	21	1	2	..
Urinary	..	2	..	2	2
Gynecological	..	12	..	..	..
Prostate	1	37*	..	1	1
Lymphoma	3	..	1	..	3
Miscellaneous	3	8	3	10	5

*Antemortem undetected primary not specified.
①Fitzpatrick and Kotalik (1974)
②Nussbaum (1973)
③Copeland and McBride (1973)
④Moertel et al (1972)
⑤University of Washington

cancer. All long-term survivors presented with cervical adenopathy and were treated as primary cancers of the pharynx.

Subsequent Identification of the Primary Cancer

Autopsy examinations were carried out on 22 patients. In three of these, a primary tumor could not be identified. In three other patients, the primary tumor site was detected before death. Therefore, a correlation of precocious metastases and primary tumor sites can be made in 22 patients (Table 3). The most frequent primary site was lung (nine patients) despite apparently nondiagnostic findings on x-ray studies of the chest.

Data from the literature regarding the ultimate identification of an initially undetected primary cancer have been summarized in Table 4.[5-8]

Discussion

Patients with metastases from undetected primary cancer usually are greeted with limited enthusiasm by physicians. Their care often is cursory and is restricted to the treatment of metastases producing immediate clinical problems. Although extended, costly investigation may result in identification of a primary tumor, such activity usually has been considered futile. This long-standing attitude by physicians needs to be reexamined for several reasons: (1) Cervical node metastases may be associated with a primary head and neck tumor which is curable (for example, carcinoma of the nasopharynx or pharyngeal tongue); (2) Specification of the primary site may lead to better directed chemotherapy or endocrine manipulation (for example, kidney, prostate and the three cases of unsuspected lymphoma); (3) Identification of the primary site may aid in anticipating problems (for example, bowel obstruction from carcinoma of the colon), and (4) Definition of the primary site can help in assessing the prognosis for the patient and family.

REFERENCES

1. Rubin P, Green J: Solitary Metastases. Springfield, IL, Charles C Thomas, Publisher, 1968
2. France CJ, Lucas RJ: The management and prognosis of metastatic neoplasms of the neck with an unknown primary. Am J Surg 106:835-839, 1963
3. MacComb WS: Diagnosis and treatment of metastatic cervical cancerous nodes from an unknown primary site. Am J Surg 124:441-449, 1972
4. Jesse RH, Perez CA, Fletcher GH: Cervical lympth node metastasis: Unknown primary cancer. Cancer 31:854-859, 1973
5. Fitzpatrick PJ, Kotalik JF: Cervical metastasis from an unknown primary tumor. Radiology 110:659-663, 1974
6. Nussbaum M: Carcinoma of prostatic origin, metastatic to cervical nodes. NY State J Med 73:2050-2054, 1973
7. Copeland EM, McBride CM: Axillary metastases from unknown primary sites. Ann Surg 178:25-27, 1973
8. Moertel CG, Reitemeier RJ, Schutt AJ, et al: Treatment of the patient with adenocarcinoma of unknown origin. Cancer 30: 1469-1472, 1972

Refer to: Earle J: Thyroid cancer—Delayed effects of head and neck irradiation in children (Medical Information). West J Med 123:340, Oct 1975

Thyroid Cancer

Delayed Effects of Head and Neck Irradiation in Children

JOHN EARLE, MD
Stanford

THE INCREASED RISK of thyroid abnormalities, particularly of thyroid carcinoma, has been brought to the attention of the medical profession.[1-6] These reports have been summarized in the daily press or brought to the attention of the public by the medical profession. The "endemic" in the Chicago area has prompted the Illinois State Medical Society and the Illinois Hospital Association to mount a widespread public education campaign which has further alerted patients to the existence of this problem. Physicians will increasingly be asked to deal with such patients.

A recent analysis of the Chicago experience provides data upon which to base a rational approach to the problem. Arnold and co-workers[4] report on 1,452 persons with a history of x-ray therapy to the neck region for benign diseases 18 to 35 years ago. All patients had relevant history taken, physical examination and ^{99m}Tc pertechnetate scintigraphy. In 21 percent of the patients, thyroid abnormalities were found. In 193 for whom surgical exploration was carried out, thyroid malignancies were found in 29 percent. Most important, for management purposes, they present data which show that in 13 of 68 patients in whom palpatory findings were normal or equivocal, there were abnormal thyroid scans and thyroid carcinoma.

Consequently, it would seem reasonable to recommend a thorough history, physical examination and thyroid scan in persons exposed to ionizing irradiation to the head and neck region as children. Abnormalities should be thoroughly evaluated with a view to their possibly being malignant. Patients in whom findings show no abnormalities should be followed with at least physical examination annually. Patients in whom findings are equivocal should be followed at shorter intervals.

Dr. Earle is Assistant Professor and Associate Director, Radiation Therapy Division, Stanford University Hospital, and a member of the Scientific Advisory Panel on Radiology of the California Medical Association. This report was written at the Advisory Panel's request.

Reprint requests to: John D. Earle, MD, Radiation Therapy Division, Stanford Medical Center, Stanford, CA 94305.

REFERENCES

1. De Groot L, Paloyan E: Thyroid carcinoma and radiation—A Chicago endemic. JAMA 225:487-491, Jul 30, 1973
2. Modan B, Baidatz D, Mart H, et al: Radiation-induced head and neck tumours. Lancet 1:277-279, Feb 1974
3. Refetoff S, Harrison J, Karanfilski BT, et al: Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N Engl J Med 292:171-175, Jan 23, 1975
4. Arnold J, Pinsky S, Ryo UY, et al: ^{99m}Tc pertechnetate thyroid scintigraphy in patients predisposed to thyroid neoplasms by prior radiotherapy to the head and neck. Radiology 115:653-657, 1975
5. Colman M, Arnold JE, Ung YR, et al: Thyroid cancer associated with irradiation to neck region in childhood—Preliminary report of a follow-up of 5,000 patients at risk. Presented to the American Society of Therapeutic Radiologists, Key Biscayne, Oct 1974
6. Colman M, Simpson LR, Patterson LK, et al: Irradiation of the neck during childhood: An assessment of factors which influence the development of thyroid tumors in persons at risk. Presented to the Radiology Research Society, Miami Beach, May 1975

CALIFORNIA
MEDICAL ASSOCIATION

105th Annual Session

February 6-11, 1976 • Hyatt Regency and Sheraton-Palace Hotels, San Francisco

PLAN TO ATTEND

PROGRAMS

- Cancer of the GI tract: the gut issues
- Current misconceptions about anxiety
- Sexuality: an essential dimension in patient care
- Neurological problems of the school-age child
- Early intervention in neuromuscular disorders
- Rheumatoid disease in childhood
- Myelomeningocele
- Everything you always wanted to know about a thyroid nodule but were afraid to ask
- Electroconvulsive therapy controversy
- Thyroid cancer
- The cornea
- Repair of eyelids after trauma
- Common problems in allergy and dermatology
- Special problems in asthma
- Athletic injuries
- Environmental and occupational impact on the lung
- Sexual desire and ability with drug use
- New trends in Dx of pancreatic and biliary lesions
- Urologic plastic surgery
- Skin problems of women
- Adolescent medicine and sexuality
- Death and dying—How to avoid a "cop out"

"MEET THE PROFESSOR" LUNCHEONS EACH DAY

WORKSHOPS

- Ear, nose and throat problems of children
- Plastic surgery suturing techniques

AFFILIATED MEETINGS

- American Cancer Society, California Division
- American College of Physicians, Northern California Region
- California Association on Ophthalmology
- California Society for the Treatment of Alcoholism and Other Drug Dependence
- California Society of Allergy and Clinical Immunology
- California Tumor Tissue Registry

OVER ONE HUNDRED SCIENTIFIC AND TECHNICAL EXHIBITS

46th Annual Convention—Woman's Auxiliary to California Medical Association

CALIFORNIA MEDICAL ASSOCIATION HOUSE OF DELEGATES

in memoriam

Baker, Charles P., Oakland. Died June 11, 1975 in Oakland of heart disease, aged 71. Graduate of the University of Nebraska College of Medicine, Omaha, 1930. Licensed in California in 1945. Dr. Baker was a member of the Alameda-Contra Costa Medical Association.

Beigelman, Maurice N., Los Angeles. Died June 20, 1975 in Los Angeles of cardiovascular accident as a result of cerebral arteriosclerosis, aged 79. Graduate of Uniwersytet Jozfa Pilsudskiego, Warszawa, 1920. Licensed in California in 1924. Dr. Beigelman was a retired member of the Los Angeles County Medical Association.

Bell, John C., Los Angeles. Died April 28, 1975. It was incorrectly reported in the August issue that Dr. Bell was a graduate of College of Osteopathic Medicine and Surgery, Des Moines. His school, rather, was College of Osteopathic Physicians and Surgeons, Los Angeles. He was 72.

Boehm, Marie Lenore, Riverside. Died June 30, 1975 in Riverside, aged 85. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1927. Licensed in California in 1928. Dr. Boehm was a retired member of the Napa County Medical Society.

Boelter, Muriel Daphne Diana, Berkeley. Died August 15, 1975 in Oakland of cerebrovascular accident, aged 60. Graduate of the University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1945. Dr. Boelter was a member of the Alameda-Contra Costa Medical Association.

Coleman, LeGrand L., Oakland. Died July 4, 1975, aged 74. Graduate of Howard University College of Medicine, Washington, DC, 1931. Licensed in California in 1937. Dr. Coleman was a member of the Alameda-Contra Costa Medical Association.

Dahle, Ben Maurice, Carmel. Died July 13, 1975 of heart disease, aged 54. Graduate of Marquette University School of Medicine, Milwaukee, 1946. Licensed in California in 1949. Dr. Dahle was a member of the Monterey County Medical Society.

Daitch, Maurice L., Los Angeles. Died May 27, 1975 in Los Angeles of cardiopulmonary failure as a result of medullary depression, aged 56. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. MD degree from California College of Medicine, 1962. Dr. Daitch was a member of the Los Angeles County Medical Association.

Dakin, Wirt Bradley, Los Angeles. Died May 24, 1975 in Los Angeles, aged 91. Graduate of the College of Medicine, University of Southern California, Los Angeles, 1908. Licensed in California in 1909. Dr. Dakin was a member of the Los Angeles County Medical Association.

Diamant, Bernard, Stockton. Died June 27, 1975 in Stockton, aged 38. Graduate of Boston University School of Medicine, 1962. Licensed in California in 1968. Dr. Diamant was a member of the San Joaquin County Medical Society.

Dwiggins, Jack Harlan, Menlo Park. Died May 23, 1975, aged 55. Graduate of the University of Arkansas School of Medicine, Little Rock, 1942. Licensed in California in 1946. Dr. Dwiggins was a member of the Santa Clara County Medical Society.

Felsen, Louis, Los Angeles. Died June 17, 1975 in Caracas, Venezuela, aged 88. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1918. Licensed in California in 1918. Dr. Felsen was a retired member of the Los Angeles County Medical Association.

Fishbein, A. Allan, San Francisco. Died August 19, 1975 in San Francisco, aged 66. Graduate of the University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1937. Dr. Fishbein was a member of the San Francisco Medical Society.

Fishman, Sidney A., Santa Monica. Died June 3, 1975 in Santa Monica of malignant melanoma, aged 61. Graduate of New York University College of Medicine, New York, 1936. Licensed in California in 1946. Dr. Fishman was a member of the Los Angeles County Medical Association.

Fogle, Jimmy L., Sausalito. Died June 22, 1975 in San Rafael, aged 36. Graduate of Baylor University College of Medicine, Houston, 1964. Licensed in California in 1969. Dr. Fogle was a member of the Marin Medical Society.

Frame, Paul W., jr., Sacramento. Died July 18, 1975 of injuries received in automobile accident near Sonora, aged 54. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1945. Licensed in California in 1946. Dr. Frame was a member of the Sacramento County Medical Association.

Frantz, Kieffer E., Beverly Hills. Died May 11, 1975 in Sherman Oaks of acute myocardial infarction, aged 64. Graduate of the University of Illinois College of Medicine, Chicago, 1940. Licensed in California in 1946. Dr. Frantz was a member of the Los Angeles County Medical Association.

FREEMAN, NORMAN E., San Francisco. Died August 9, 1975 of heart disease, aged 72. Graduate of Yale University School of Medicine, New Haven, 1928. Licensed in California in 1946. Dr. Freeman was a member of the San Francisco Medical Society.

GAMETTE, DOUGLAS LEON, Los Angeles. Died August 12, 1975 in South Laguna, aged 79. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1921. Licensed in California in 1927. Dr. Gamette was a member of the Los Angeles County Medical Association.

GERSTLE, MARK L., San Francisco. Died August 1, 1975 in San Francisco, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr. Gerstle was a member of the San Francisco Medical Society.

GLASCOCK, FRED LEIB, Carmel Valley. Died July 9, 1975 in Carmel Valley, aged 86. Graduate of Rush Medical College, Chicago, 1916. Licensed in California in 1923. Dr. Glascock was a retired member of the Los Angeles County Medical Association.

GUARDINO, SALVATOR J., Brisbane. Died August 6, 1975, aged 68. Graduate of the Creighton University School of Medicine, Omaha, 1930. Licensed in California in 1930. Dr. Guardino was a member of the San Mateo County Medical Society.

GULDSETH, GUSTAV DANIEL, Hemet. Died January 18, 1975 of adenocarcinoma of the intestine, aged 40. Graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, 1966. Licensed in California in 1967. Dr. Guldseth was a member of the Riverside County Medical Association.

HERSHEY, PETER, Huntington Park. Died June 12, 1975 in Los Angeles of acute myocardial infarction, aged 74. Graduate of Magyar Királyi Erzébet Tudományegetyetem Orvostudományi, Pécs, 1926. Licensed in California in 1943. Dr. Hershey was a member of the Los Angeles County Medical Association.

HORWITZ, MORIS, Encino. Died May 30, 1975 in Encino of heart disease, aged 61, Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1943. Dr. Horwitz was a member of the Los Angeles County Medical Association.

HOYER, E. CHARLES, Escondido. Died June 24, 1975 in Escondido, aged 63. Graduate of Northwestern University Medical School, Chicago, 1938. Licensed in California in 1958. Dr. Hoyer was a member of the San Diego County Medical Society.

JACOBS, JOHN THEODORE, JR., Oceanside. Died August 9, 1975 of heart disease, aged 71. Graduate of the University of Colorado School of Medicine, Denver, 1932. Licensed in California in 1933. Dr. Jacobs was a member of the San Diego County Medical Society.

KELLEY, HARRY WARNER, Oakland. Died August 12, 1975 in Oakland of heart disease, aged 73. Graduate of the University of Minnesota Medical School, Minneapolis, 1930. Licensed in California in 1931. Dr. Kelley was a member of the Alameda-Contra Costa Medical Association.

MARASCO, FRED BERNARD, San Francisco. Died July 2, 1975, aged 68. Graduate of the University of Colorado School of Medicine, Denver, 1934. Licensed in California in 1936. Dr. Marasco was a member of the San Francisco Medical Society.

MARUBAYASHI, STANLEY T., Orange. Died August 15, 1975 in Santa Ana of injuries received in a traffic accident, aged 50. Graduate of the Creighton University College of Medicine, Omaha, 1952. Licensed in California in 1954. Dr. Marubayashi was a member of the Orange County Medical Association.

MAXWELL, RALPH EARL, Pacific Grove. Died July 18, 1975 in Carmel, aged 84. Graduate of Vanderbilt University School of Medicine, Nashville, 1917. Licensed in California in 1917. Dr. Maxwell was a member of the Monterey County Medical Society.

MCCLURE, JAMES CLIFTON, Exeter. Died June 15, 1975 of glioma of the brain, aged 78. Graduate of the University of Michigan Medical School, Ann Arbor, 1922. Licensed in California in 1923. Dr. McClure was a member of the Tulare County Medical Society.

MICHELSON, LEWIS, Stanford. Died July 5, 1975 in San Francisco, aged 90. Graduate of Cooper Medical College, San Francisco, 1907. Licensed in California in 1908. Dr. Michelson was a retired member of the San Francisco Medical Society.

NEWEL, CLARENCE D., Fresno. Died May 30, 1975 in Fresno, aged 72. Graduate of the State University of Iowa College of Medicine, Iowa City, 1930. Licensed in California in 1935. Dr. Newel was a retired member of the Fresno County Medical Society.

OHANNESON, JOHN, Alameda. Died June 27, 1975 in Oakland of brain tumor lymphoma, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr. Ohanneson was a retired member of the Alameda-Contra Costa Medical Association.

PENNINGTON, ALMA STEVENS, San Francisco. Died February 19, 1975 of myocardial infarction, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Dr. Pennington was a retired member of the San Francisco Medical Society.

SCHWEIFLER, JOHN, San Francisco. Died August 4, 1975 in San Francisco, aged 62. Graduate of Marquette University School of Medicine, Milwaukee, 1943. Licensed in California in 1943. Dr. Schweifler was a member of the San Francisco Medical Society.

SHUBIN, STANLEY HERBERT, Los Angeles. Died June 29, 1975 near Mammoth Lake of heart disease, aged 50. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1951. Licensed in California in 1951. Dr. Shubin was a member of the Los Angeles County Medical Association.

SMITH, STEWARD H., San Diego. Died January 31, 1975 of Hodgkin's disease, aged 61. Graduate of Harvard Medical School, Boston, 1939. Licensed in California in 1946. Dr. Smith was a member of the San Diego County Medical Society.

SMITHIES, HAROLD RIDDIOUGH, Oakland. Died July 27, 1975 in Oakland of heart disease, aged 78. Graduate of the University of Colorado School of Medicine, Denver, 1925. Licensed in California in 1928. Dr. Smithies was a retired member of the Alameda-Contra Costa Medical Association.

SWEENEY, JOHN PAUL, San Mateo. Died May 26, 1975 in San Mateo, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Dr. Sweeney was a retired member of the San Mateo County Medical Society.

TALBOTT, GRACE M. (GRACE TALBOTT BOVILL), San Francisco. Died August 26, 1975, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Dr. Talbott was a retired member of the San Francisco Medical Society.

THEBAUT, WILLIAM MAXWELL, JR., Oakland. Died July 8, 1975, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Dr. Thebaut was a member of the Alameda-Contra Costa Medical Association.

ULRICH, GEORGE JOHN, Santa Barbara. Died July 8, 1975 in Santa Barbara of cancer, aged 64. Graduate of the University of Maryland School of Medicine, Baltimore, 1941. Licensed in California in 1945. Dr. Ulrich was a member of the Santa Barbara County Medical Society.

VAN SICKLIN, ROY, Fresno. Died July 16, 1975, aged 65. Graduate of Northwestern University Medical School, Chicago, 1942. Licensed in California in 1953. Dr. Van Sicklin was a member of the Fresno County Medical Society.

WALIGORA, DANIEL JOHN, Monterey. Died December 5, 1974 of myocardial infarction, aged 66. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in California in 1951. Dr. Waligora was a member of the Monterey County Medical Society.

WANLESS, JOHN, F., San Diego. Died June 19, 1975, aged 64. Graduate of the University of Wisconsin Medical School, Milwaukee, 1938. Licensed in California in 1946. Dr. Wanless was a member of the San Diego County Medical Society.

WATSON, JAMES LOWELL, Palo Alto. Died June 22, 1975 in Mountain View of cancer, aged 66. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1936. Licensed in California in 1945. Dr. Watson was a member of the Santa Clara County Medical Society.

WOLFE, NATHALIE M., Fresno. Died August 16, 1975, aged 55. Graduate of New York Medical College, New York, 1943. Licensed in California in 1946. Dr. Wolfe was a member of the Fresno County Medical Society.

WONG, ARNOLD VARDOC, Lynwood. Died in June 1975, aged 46. Graduate of the University of California Medical School, Berkeley-San Francisco, 1955. Licensed in California in 1956. Dr. Wong was a member of the Los Angeles County Medical Association.

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

November 7-8—**San Francisco Cancer Symposium of 1975—Current Concepts of Cancers Occurring in the Neck and in the Female Genital Tract.** Claire Zellerbach Saroni Tumor Institute of Mt. Zion Hospital and Medical Center, San Francisco. $150. Friday-Saturday. Contact: Dept. of Cont. Ed., Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120.

November 14-15—**Breast Cancer: Its Impact on the Patient, Family and Community.** West Coast Cancer Foundation; Univ. of the Pacific, School of Medical Sciences; St. Mary's Hospital and Med. Ctr.; PMC, Dept. of Psychological & Social Medicine, at Hyatt Regency, San Francisco. Friday-Saturday. $75 if registered before Nov. 1; $90, late registration. Contact: Jerome M. Vaeth, MD, Dir., WCCF, 2340 Clay St., P.O. Box 7999, San Francisco 94120. (415) 563-5213.

November 22—**Practical Oncology.** UCD. Saturday.

December 7—**Seminar on Head and Neck Tumors—Semi-Annual.** California Tumor Tissue Registry, Hyatt Hotel, San Francisco. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

MEDICINE

October 15-17—**Diabetes and Related Endocrine Diseases.** UCSF. Wednesday-Friday.

October 15-19—**American Association for Clinical Immunology and Allergy.** Riviera Hotel, Palm Springs. Wednesday-Sunday. Contact: Howard Silber, AACIA, P.O. Box 912, DTS, Omaha, Neb. 68101. (402) 558-5345.

October 18-19—**Dermatologic Surgery.** See Surgery, October 18-19.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** See Of Interest To All, October 18-19.

October 25—**A Practical Approach to Respiratory Care.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

October 26-30—**American College of Chest Physicians—41st Annual Scientific Assembly.** Disneyland Hotel, Anaheim. Sunday-Thursday, Contact: Alfred Soffer, MD, Exec. Dir., ACCP, 911 Busse Highway, Park Ridge, Ill. 60068. (312) 698-2200.

November 10-14—**Pediatric Allergy and Clinical Immunology—11th Annual Workshop.** UCSF. Monday-Friday.

November 13—**Lung Association of Contra Costa and Solano Counties—Physicians' Postgraduate Course.** Sheraton Inn, Concord. Thursday. Contact: Pat Gilman, 105 Astrid Dr., Pleasant Hill 94523. (415) 935-0472.

November 15—**Pediatric Dermatology.** Childrens Hospital of Orange County, Orange. Saturday. Contact: Merl J. Carson, MD, Med. Dir., CHOC, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

November 15-18—**Gastroenterology: Current Topics with Emphasis on Peptic Ulcer.** UCLA at Kona Kai Hotel, San Diego. Saturday-Tuesday.

November 16—**Heparin-Thrombosis Seminar.** American Heart Assn. Council on Thrombosis; American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Sunday. $30. Contact: Symposiums International, 130 El Camino Dr., Beverly Hills 90212. (213) 273-2157.

November 16—**Hypertension.** UCLA and Granada Hills Community Hospital at Calif. State University, Northridge. Sunday.

(Continued on Page 38)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contains natural estrogens exclusively and also meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

BRAND OF **CONJUGATED ESTROGENS TABLETS, U.S.P.**

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 35)

November 17-21—**American Heart Association.** Disneyland Hotel, Anaheim. Monday-Friday. Contact: William W. Moore, Exec. V. P., AHA, 44 E. 23rd St., N.Y. 10010.

November 19-21—**Practical Electrocardiography—Chungs' Approach.** Memorial Hospital Medical Center, UCI Center for Health Education, Long Beach. Wednesday-Friday. $150. Contact: Donald K. Chung, MD, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 19-21—**Respiratory Failure.** USC. Friday-Sunday.

November 20-22—**West Coast Allergy Society.** Royal Inn at the Wharf, San Diego. Thursday-Saturday. Contact: Harvey O. Randel, MD, WCAS, 2164 SW Park Pl., Portland, Ore. 97205. (503) 226-1555.

November 22—**Nuclear Cardiology.** UCSF. Saturday.

November 22—**Management of Respiratory Failure in Infants.** See Pediatrics, November 22.

November 22—**Flexible Bronchofibroscopy.** See Surgery, November 22.

December 4-6—**Rheumatic Diseases—4th Annual Western Regional Conference.** UCSF at Claremont Hotel, Oakland. Thursday-Saturday.

December 5-6—**Diabetes Mellitus.** STAN and Santa Clara County Diabetes Assn. at Rickey's Hyatt House, Palo Alto. Friday-Saturday. Contact: STAN.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** See Of Interest To All, December 5-6.

December 6—**Advances in Diabetes Mellitus, Calcium and Water Disorders.** Daniel Freeman Memorial Hospital at International Hotel, Los Angeles. Saturday. $35. Contact: Joan Covell, Med. Staff Sec., Daniel Freeman Memorial Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 672-0112, ext. 206.

December 6—**The Asthmatic.** UCLA. Saturday.

December 6-11—**American Academy of Dermatology.** Hilton Hotel, San Francisco. Saturday-Thursday. Contact: Betty Suor, Exec. Dir., AAD, 1116 S. Fifth, Tacoma, Wa. 98405. (206) 572-4747.

December 7-9—**Advances in Heart Disease—1976.** American College of Cardiology at Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 10—**Colloquia in Cardiology—No. 8: Stress and the Heart—The Influence and Management of Stress in Heart Disease.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

MENTAL RETARDATION

October 30-31—**Mental Retardation.** USC. Thursday-Friday.

OBSTETRICS AND GYNECOLOGY

October 15-19—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 31 hrs. $15 for members; $25, non-members. Contact: Ms. Dee Davis, Exec. Sec., PCFS, 5410 Wilshire Blvd., Suite 600, Los Angeles 90036. (213) 937-5514.

October 18—**Office Management of Common Gynecological Disorders.** Palo Alto Medical Clinic, Palo Alto. Saturday. Contact: William D. McKee, MD, Dept. of Allergy, Palo Alto Med. Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

(Continued on Page 40)

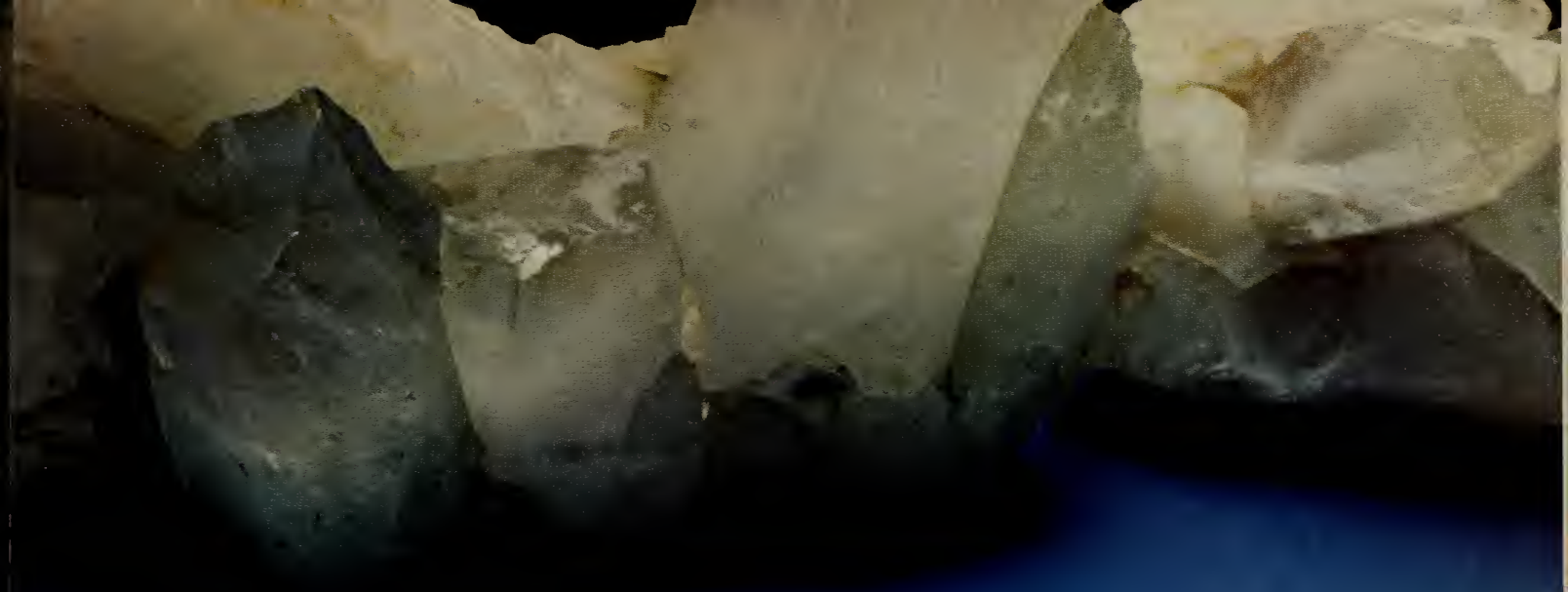
PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing witho prescription.
Description. Proloid (thyroglobulin) is obtain from a purified extract of frozen hog thyroid. It co tains the known calorigenically active component Sodium Levothyroxine (T_4) and Sodium Liothyr nine (T_3). Proloid (thyroglobulin) conforms to t primary USP specifications for desiccated thyroid for iodine based on chemical assay—and is al biologically assayed and standardized in animal
Chromatographic analysis to standardize the S dium Levothyroxine and Sodium Liothyronine co tent of Proloid (thyroglobulin) is routinely employe
The ratio of T_4 and T_3 in Proloid (thyroglobuli is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid r placement therapy for conditions of inadequate e dogenous thyroid production: e.g., cretinism a myxedema. Replacement therapy will be effecti only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglob lin) may be tried therapeutically, in nonemergen situations, in an attempt to reduce the size of suc goiters.
Contraindication. Thyroid preparations are contr indicated in the presence of uncorrected adren insufficiency.
Warnings. Thyroglobulin should not be used in th presence of cardiovascular disease unless thyroi replacement therapy is clearly indicated. If the la ter exists, low doses should be instituted beginnin at 0.5 to 1.0 grain (32 to 64 mg) and increased b the same amount in increments at two-week inte vals. This demands careful clinical judgment.
Morphologic hypogonadism and nephrose should be ruled out before the drug is adminis tered. If hypopituitarism is present, the adrenal de ficiency must be corrected prior to starting the dru
Myxedematous patients are very sensitive to th roid and dosage should be started at a very lo level and increased gradually.
Precaution. As with all thyroid preparations th drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid in crease in dosage may result in signs and symptom of hyperthyroidism, such as menstrual irregular ties, nervousness, cardiac arrhythmias, and angin pectoris.
Dosage and Administration. Optimal dosage i usually determined by the patient's clinical re sponse. Confirmatory tests include BMR, $T_3{}^{131}$ resin sponge uptake, $T_3{}^{131}I$ red cell uptake, Thyr Binding Index (TBI), and Achilles Tendon Refle Test. Clinical experience has shown that a norma PBI (3.5-8 mcg/100 ml) will be obtained in patient made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started i small amounts and increased gradually with incre ments at intervals of one to two weeks. Usual main tenance dose is 0.5 to 3.0 grains (32 to 190 mg daily.
Instructions for Use. The following conversio table lists the approximate equivalents of othe thyroid preparations to Proloid (thyroglobulin) whe changing medication from desiccated thyroid, T_4 (sodium levothyroxine), T_3 (sodium liothyronine), o T_4/T_3 (liotrix).

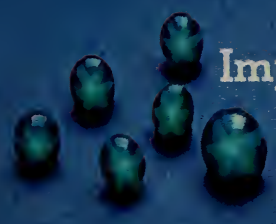
CONVERSION TABLE

Dose of Proloid (thyroglobulin)	Dose of Desiccated Thyroid	Dose of T_4 (sodium levothyroxine)	Dose of T_3 (sodium liothyronine)	Dose of liotrix (T_4/T_3)
1 grain	1 grain	0.1 mg	25 mcg	#1 (60 mcg/15 mcg
2 grains	2 grains	0.2 mg	50 mcg	#2 (120 mcg/30 mcg
3 grains	3 grains	0.3 mg	75 mcg	#3 (180 mcg/45 mcg
4 grains	4 grains	0.4 mg	100 mcg	
5 grains	5 grains	0.5 mg	125 mcg	

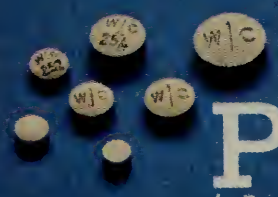
In changing from Thyroid USP to Proloid (thyroglobulin), substitute the equivalent dose of Proloid (thyroglobulin). Each patient may still require fine adjustment of dosage because the equivalents are only estimates.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
Supplied. ¼ grain tablets in bottles of 100 (N 0047-0250-51) and 1000 (N 0047-0250-60); ½ grain tablets in bottles of 100 (N 0047-0251-51) and 1000 (N 0047-0251-60); scored 1 grain tablets in bottles of 100 (N 0047-0252-51) and 1000 (N 0047-0252-60); 1½ grain tablets in bottles of 100 (N 0047-0253-51) and 1000 (N 0047-0253-60); scored 2 grain tablets in bottles of 100 (N 0047-0257-51); 3 grain tablets in bottles of 100 (N 0047-0254-51) and 1000 (N 0047-0254-60); scored 5 grain tablets in bottles of 100 (N 0047-0255-51) and 1000 (N 0047-0255-60). Full information is available on request. P-GP-51 4/-

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, N.J. 07950





Improving on nature...
from the rough, uncut stone
to the finished gem



In thyroid therapy, too...
all the qualities of the "natural" with the
added improvements of man...

Proloid®
(thyroglobulin)

natural thyroid...but uniquely purified
Devoid of any glandular debris.

natural thyroid...but triply standardized
Standardized chemically, biologically, and (at intervals) clinically, for consistent metabolic activity from batch to batch.

natural thyroid...but consistently fresh
Potency undiminished for up to 4 years under proper storage conditions.

It all adds up to natural thyroid with the added improvements of man.

Please see adjoining column for brief summary of prescribing information.

(Continued from Page 38)

October 20-24—**Ob/Gyn Review.** USC. Monday-Friday.

October 24-25—**Perinatal Neurology.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday.

October 31—**Advances in Gynecology.** Northern California Ob-Gyn Society at Sacramento. Friday. Contact: Solon Barbis, MD, 1816 Professional Dr., Sacramento 95825.

November 14-15—**Breast Cancer: Its Impact on the Patient, Family and Community.** See Cancer, November 14-15.

December 13-14—**Birth and Rebirth.** UC Extension, Santa Cruz. Saturday-Sunday. 15 hrs. $40. Contact: Darla Chadima, Cont. Ed. Specialist, UC Extension, Santa Cruz 95064. (408) 429-2971.

PEDIATRICS

November 6-7—**Pediatric Dialysis.** USC. Thursday-Friday.

November 8—**Caregiving for Infants During the First Two Years of Life—2nd Annual Child Development Conference.** UCLA. Saturday.

November 10-14—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 10-14.

November 11-13—**Pediatric and Adolescent Aspects of Trauma.** USC at Gene Autry Hotel, Palm Springs. Tuesday-Thursday.

November 15—**Pediatric Dermatology.** See Medicine, November 15.

November 22—**Management of Respiratory Failure in Infants.** Harbor General Hospital, Torrance. Saturday. 6 hrs. $45. Contact: Ellen Woolfson, Cont. Ed. Coordinator, Torrance General Hospital, 1124 W. Carson A-19, Torrance 90502. (213) 775-7711, ext. 1373.

December 6—**American Academy of Pediatrics, California Chapter 1, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

PSYCHIATRY

November 10-14—**Group Therapy Seminars.** UCSF at Leamington Hotel, Oakland. Monday-Friday.

December 10-13—**Development of Techniques for Family Counseling.** See Of Interest To All, December 10-13.

RADIOLOGY AND PATHOLOGY

September 20—**Nuclear Medicine Symposium — Imaging the Head.** Nuclear Medicine Section of Memorial Hospital Association at Holiday Inn (1612 Dale Road, on U.S. 99), Modesto. Saturday. No fee. Contact: Darrell K. Oberg, MD, 600 Coffee Rd., Modesto 95355. (209) 524-1211.

September 27—**Current Topics in Diagnostic Radiology.** Southern California Permanente Medical Group at Marriott Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 27-28—**Nuclear Medicine.** UCLA. Saturday-Sunday.

September 27-28—**New Scintigraphic Procedures for Tumor Diagnosis.** UCLA. Saturday-Sunday.

October 8-12—**American Society of Therapeutic Radiologists.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Sheila McGing, Exec. Sec., ASTR, 20 N. Wacker Dr., Room 2920, Chicago, Ill. 60606.

October 20-24—**Pathology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

November 7-9—**Modern G. U. Radiology—The Practical Approach (9th Annual Leo G. Rigler Symposium).** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday.

December 3-7—**California Society of Pathologists—Annual Meeting.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Mr. Richard E. Hall, CSP, 1225 8th St., Suite 590, Sacramento 95814. (916) 446-6001.

December 12—**Principles and Procedures of Blood Gases.** PMC. Saturday. $65.

December 12-14—**Fluid and Electrolytes.** USC at Tennis Club, Palm Springs. Friday-Sunday.

SURGERY AND ANESTHESIOLOGY

October 16—**Anesthesiology.** Cedars-Sinai Medical Center, Los Angeles. Thursday. Contact: Mrs. Linda Alperstein, Coord., Cont. Med. Ed., Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111.

October 18-19—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

October 21-December 2—**Surgical Anatomy and Surgery.** USC. Tuesdays.

October 24-25—**Retinal Symposium.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

October 24-25—**Orthopaedic Seminar: Management of Spine Pain.** Eisenhower Medical Center, Palm Desert. Friday-Saturday. 6 hrs. $50. Contact: Office of Medical Education & Research. Eisenhower Medical Center, 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

October 24-26—**Western Neurological Society.** Biltmore Hotel, Santa Barbara. Friday-Saturday. Contact: Calvin L. Rumbaugh, MD, or Hervey D. Segall, MD, L.A. County-USC Med. Center, 1200 N. State St., Los Angeles 90033. (213) 226-7425.

October 26-30—**Western Orthopedic Association.** Hilton Hotel, San Francisco. Sunday-Thursday. 18 hrs. Contact: H. Jacqueline Martin, Exec. Sec., WOA, 1970 Broadway, Suite 1235, Oakland 94612. (415) 893-1257.

November 3-5—**Hereditary Disorders of the Eye—Annual Ophthalmology Course.** UCSF. Monday-Wednesday.

November 6-7—**Neurological Infections: New Clinical Approaches.** UCSF at VA Hospital, San Francisco. Thursday-Friday.

November 6-7—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

November 7-8—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

November 8—**Cleft Palate and Cranio-Facial Anomalies—7th Annual Symposium.** St. John's Hospital and Health Center, Santa Monica. Saturday. Contact: Kathy Harding, Asst. Coord,. Cleft Palate Service, St. John's Hospital and Health Center, 1328 22nd St., Santa Monica 90404. (213) 829-5511, ext. 2745.

November 8-9—**Muscle Relaxants.** American Society of Anesthesiologists at Marriott Hotel, Los Angeles. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

November 11-13—**Pediatric and Adolescent Aspects of Trauma.** See Pediatrics, November 11-13.

November 12—**Acute Care in Medical Management of Spinal Cord Injured.** Calif. Regional Spinal Cord Injury Care System, Santa Clara Valley Medical Center, San Jose. Wednesday. 8 hrs. $50. Contact: Melinda Miller, SCVMC, 751 S. Bascom Ave., San Jose 95128. (408) 293-0262, ext. 421.

November 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 13-15—**Infections in Orthopedics.** STAN. Thursday-Saturday.

November 15—**Current Concepts in Ophthalmic Plastic Surgery: The Eye Lid.** UCLA. Saturday.

November 21-23—**Common Problems—Acute Hand Injuries.** UCLA. Friday-Sunday.

November 22—**Flexible Bronchofibroscopy.** PMC. Friday. 6 hrs. $300.

December 3-5—**Hereditary Disorders of the Eye—Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

December 5—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. $150. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** See Of Interest To All, December 5-6.

December 5-7—**Electronystagmography.** PMC at Regency Hyatt, San Francisco. Friday-Saturday.

December 5-9—**International College of Surgeons, U.S. Section —Annual Meeting.** Sheraton Waikiki, Honolulu. Friday-Tuesday. Contact: Mr. William A. Houser, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago. Ill. 60610. (312) 642-3555.

December 10-12—**Ocular Inflammatory Disease.** USC. Wednesday-Friday.

December 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

October 16-17—**Immunology for the Practicing Physician.** UCSF at Kaiser Center Auditorium, 300 Lakeside Dr., Oakland. Thursday-Friday.

October 17—**Antiplatelet Drugs and Thrombosis.** PMC at Miyako Hotel, San Francisco. Friday.

October 18-19—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

October 18-19—**Review of Antimicrobial Therapy.** UCLA. Saturday-Sunday.

November 3, 4—**Death and Dying.** Eskaton American River Healthcare Center, Carmichael. Monday or Tuesday. $30. Contact: Roberta DeFrantz, RN, Dir., Staff Development, Eskaton American River Healthcare Center, 4747 Engle Rd., Carmichael. (916) 486-3211.

November 3-7—**Intensive Care.** STAN. Monday-Friday.

November 7-8—**Sports Medicine.** USC. Friday-Saturday.

November 9-12—**California Academy of Family Physicians.** Hotel Del Coronado, Coronado. Sunday-Wednesday. Contact: Mr. William W. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

November 13-14—**New Concepts in Medicine.** California Hospital Medical Center, Los Angeles. Thursday-Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Education, CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

November 15-16—**Crises Intervention—Part I.** UCLA. Saturday-Sunday.

November 20-22—**American Association for Automotive Medicine.** Sheraton Harbor Island, San Diego. Wednesday-Saturday. Contact: Albert Carriere, 801 Green Bay Rd., Lake Bluff, Ill. 60044.

November 30-December 4—**American Medical Association—29th Clinical Convention.** Sheraton Waikiki, Honolulu. Sunday-Thursday. Contact: AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

December 4-6—**Rheumatic Diseases—4th Annual Western Regional Conference.** UCSF at Claremont Hotel, Oakland. Thursday-Saturday.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** Eisenhower Medical Center, Palm Desert. Friday-Saturday. 8 hrs. $50. Contact: Office of Medical Education, Eisenhower Medical Center, Palm Desert 92260. (714) 346-3911.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD. Monday-Friday.

December 10-13—**Development of Techniques for Family Counseling.** UCLA at Marina City Club, Marina Del Rey. Wednesday-Saturday.

December 13-14—**Crises Intervention—Part II.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

October 15—**Adolescence and Its Problems.** Portland, Civic Auditorium. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

October 16—**The Psychology of Weight Loss.** Portland, Assembly Hall, Memorial Coliseum. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

November 7—**The Practical Management of the Patient with Coronary Disease.** Portland, Nursing Auditorium, Good Samaritan Hospital. Contact: S. Spence Meighan, MD, 1015 N.W. 22nd, Portland 97210, (503) 229-7137.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

October 14-19—**American Society of Clinical Hypnosis Annual Meeting.** Tuesday-Sunday. Washington Plaza Hotel, Seattle. Contact: Ernest T. Guy, Exec. Director, 2400 East Devon Ave., Suite 218, Des Plaines, IL 60018. (312) 297-3317.

October 17-18—**Washington State Heart Association Symposium.** Friday-Saturday. Olympic Hotel, Seattle. Fee to be determined. Contact: De Loris Savage, R.N., Wash. State Heart Assoc., 333 1st Ave. W., Seattle 98119. (206) 285-2415.

October 30-31—**Office Management of Chronic Pain.** Thursday-Friday. University Tower Hotel, Seattle. Limited to 50. 12 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 6-7—**Learning Disabilities: Dilemma and Decisions.** Thursday-Friday—Univ. of Wash. Child Development and Mental Retardation Center, Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir., CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 13-14—**Current Concepts in Drug Therapy.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. Hours to be determined. $50. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

November 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 4-5—**Life Saving Measures for the Critically Injured. (A.C.S.)** Thursday-Friday. Washington Plaza Hotel, Seattle. Limited to 200. 15 hrs. Practitioners, $150; interns, residents, $75. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

December 4-5—**Pacific Northwest Chapter, American College of Chest Physicians: Scientific Program.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 12-13—**Clinical Problems in Endocrinology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 9-10—**Laboratory Investigations in Gastrointestinal Disease.** Friday-Saturday. Virginia Mason Medical Center Auditorium. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 22-23—**Pediatric Allergy and Immunology.** Thursday-Friday. Univ. of Wash., Child Development and Mental Retardation Center, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 30-31—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Olympic Hotel, Seattle. Limited to 50 physicians and spouses. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Armour Pharmaceutical Company
Letter 3

Ayerst Laboratories
Premarin 36, 37

Boehringer Ingelheim Ltd.
Combipres 10, 11
Catapres 30, 31

Books Received 14

Classified 16, 23

Compton Foundation 16

Dairy Council of California 7

Geigy Pharmaceuticals
Butazolidin 17, 18

Eli Lilly and Company
Darvon-N 100 and Darvon Compound-65 ..... 14, 15
Keflex 24
Nebicin 32, 33, 34

Medical Ancillary Services Inc. 5

Merck Sharp & Dohme
Triavil 20, 21, 22

Obetrol Pharmaceuticals
Obetrol 19

Pharmaceutical Manufacturers Association 28, 29

PVO International
Saffola ..... 3rd Cover

A. H. Robins Company
Donnagel-PG 25
Robitussin 26, 27

Roche Laboratories
Valium ..... 2nd Cover and Page 1
Dalmane 12, 13

William H. Rorer, Inc.
Maalox ..... 4th Cover

G. D. Searle & Co.
Lomotil 2, 3

Smith Kline & French Co.
Dyazide 6

Warner Chilcott Laboratories
Proloid 38, 39

Wyeth Laboratories
Bicillin/Wycillin 8, 9

THE WESTERN
Journal of Medicine

Refer to: Burns RS, Lerner SE, Corrado R, et al: Phencyclidine —States of acute intoxication and fatalities. West J Med 123:345-349, Nov 1975

Phencyclidine — *States of Acute Intoxication and Fatalities*

R. STANLEY BURNS, MD, STEVEN E. LERNER, MS, *and* ROBBIE CORRADO, PA
San Francisco
STUART H. JAMES, BS, *Johnson City, New York*
SIDNEY H. SCHNOLL, MD, *Philadelphia*

Phencyclidine is now one of the most frequently used main ingredients of "street drug" preparations. Its effects are highly dose dependent and three varieties of acute intoxication have been seen clinically associated with different dosages and routes of administration. Most persons using phencyclidine smoke it sprinkled on parsley in low doses. The presence of horizontal and vertical nystagmus associated with hypertension in a patient who is agitated or comatose are diagnostic of a phencyclidine intoxicated state. Sensory isolation and intravenous administration of diazepam in the event of seizure activity have proved effective in the treatment of acute intoxicated states. Phencyclidine has pronounced behavioral toxicity and several deaths due to this agent have now been documented. It is unknown whether seizure activity or respiratory depression is the primary cause of death in pharmacological overdoses.

PHENCYCLIDINE (Sernyl®, Sernylan®) is 1-(1-phencyclohexyl) piperidine hydrochloride (see Figure 1). It is a white crystalline solid which is soluble in water and alcohol.

Synthesized by Parke, Davis and Company, phencyclidine was recommended for clinical trials in humans in 1957. Investigation of its effects in animals had shown a potent analgesic activity and potential use as a nonbarbiturate, nonnarcotic intravenously administered anesthetic agent was explored. Due to emergence reactions—agitation, excitement, disorientation and hallucinatory phenomena—Parke, Davis and Company in 1965 requested that further human clinical investigation be discontinued. The structurally related anesthetic ketamine was subsequently developed.

Since 1967, phencyclidine has been available for legitimate use only as an anesthetic or tranquilizing agent for primates. Currently, phencyclidine is considered a controlled dangerous substance under the Comprehensive Drug Abuse Prevention and Control Act of 1970.

Phencyclidine made its first "street" appearance in San Francisco in 1967 where it was being marketed as the "PeaCe Pill." Many persons experienced unexpected effects and phencyclidine gained a bad street reputation. It then began to appear in new guises and in combination with

From the Rock Medicine Section, Haight-Ashbury Free Medical Clinic, San Francisco (Dr. Burns, Mr. Lerner and Ms. Corrado); the Toxicology Department, Wilson Memorial Hospital, Johnson City, NY (Mr. James); and the Department of Psychiatry, University of Pennsylvania Medical School (Dr. Schnoll).

Submitted March 26, 1975.

Reprint requests to: Steven E. Lerner, MS, R. Stanley Burns, MD, & Associates, 350 Parnassus Avenue, Suite 304 A, San Francisco, CA 94117.

other drugs. Thirty different alleged street drugs analyzed during the years 1972 to 1974 contained phencyclidine.[1] The most persistent misrepresentation of phencyclidine has been as THC (tetrahydrocannabinol). Most recently, phencyclidine has been sold on the West Coast as "crystal" or "crystal joints" (CJ's).

Different patterns of phencyclidine use have emerged. First time use occurs with persons unknowingly or in an exploratory fashion smoking a cigarette made by sprinkling phencyclidine "crystals" on parsley. Although the occasional or recreational use pattern is seen, its development from this first time use is frequently interrupted by the experience of unexpected and unpleasant effects. However, several clusters of 10 to 20 persons who have shared phencyclidine daily for periods of two to six years have now been identified.

Between July 1973 and February 1974 there were in excess of 1,300 mentions nationwide of phencyclidine in the Drug Abuse Warning Network (DAWN) system. Of 86 urine samples collected during 10 months by one California police agency in cases of suspected intoxication while driving or in public, 48 were positive for phencyclidine exclusively.[2] Widespread use and availability both across the United States and Western Europe have also been reported by phencyclidine users during interviews.

Pharmacology

Phencyclidine acts primarily on the central nervous system either by stimulation or depression. Its pharmacological action in animals is complex and dependent upon both the species and the dosages.[3] The variability in activity makes it difficult to classify this agent.

The effects of phencyclidine in humans, likewise, are highly dose dependent. In clinical trials, phencyclidine proved to have a unique spectrum of activity in anesthetic dosages (0.25 mg per kg of body weight, administered intravenously). An unresponsive state with complete anesthesia was induced, although the eyes remained open (blank stare) and the patient appeared to be awake. Neither hypotension nor respiratory depression was produced by phencyclidine in anesthetic dosages. Characteristically, a moderate hypertensive response associated with tachycardia and no significant change in respiratory function was observed.

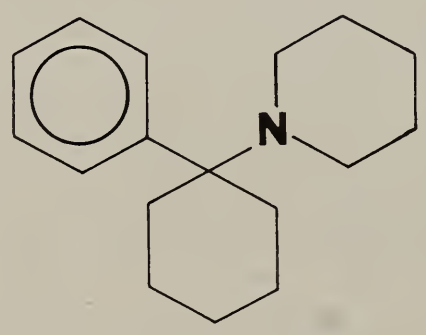


Figure 1.—Phencyclidine (1-[1-phencyclohexyl] piperidine hydrochloride).

Initial trials with the administration of higher dosages (0.5 to 1.0 mg per kg of body weight, given intravenously) showed the progressive development of severe agitation, muscle rigidity and generalized seizure activity. Respiratory depression was not seen in this dosage range.[4]

States of Acute Intoxication

The temporal profile and unique spectrum of signs and symptoms associated with different dosage ranges and different routes of administration require description of three varieties or stages of acute intoxication.

During the period April 1974 to June 1975, 55 cases of acute intoxication with phencyclidine by history were seen by the authors. Fifty-four cases represent acute intoxication states resulting from reported low to moderate doses of phencyclidine self-administered by inhalation (smoking) or insufflation ("snorting"). In one case a high dose was taken orally and the patient was comatose for a period of approximately 10 hours. Urine samples were obtained in 10 percent of the cases. Analysis by gas chromatography showed the presence of phencyclidine in all collected samples.

The clinical findings in 44 cases of low dose acute intoxication and 10 cases involving a moderate dose have been summarized in Table 1. The single case involving a high oral dose has been combined with the findings from four similar cases and the composite clinical picture is also described in Table 1.[5-8]

The low dose state is characterized by mild agitation or excitement in a patient who is grossly ataxic and has a "blank stare" appearance. Catatonic rigidity (catalepsy) may be shown, with the patient unable to speak. However, in most cases the patient is communicative and on testing horizontal and vertical nystagmus is present. Loss of

TABLE 1.—*Acute Intoxicated States*

	Low Dose (44 cases)	*Moderate Dose (10 cases)*	*High Dose (5 cases)*
Route	Inhalation (smoking)	Inhalation or insufflation	Oral
Estimated dose	5-10 mg	10-20 mg	100+ mg (approx. for adults)
Onset	2-3 minutes	2-3 minutes	45 minutes
Duration acute, symptoms	1-2 hours	Duration of coma ½-1 hour	Duration of coma 6-12 hours
Time required to recover to normal	4-8 hours	8-24 hours	48-96+ hours
State of consciousness	Communicative, or may be unable to speak; blank stare appearance; disoriented for time/place; anxious, fearful, agitated or may be mildly euphoric; restless or excited, may exhibit regressive or self-destructive behavior	Comatose or stuporous with open eyes, waking appearance; responds only to noxious stimuli (deep pain); followed by 1-2 hour period where signs and symptoms of low dose state are manifest; amnesia for period of coma/stupor	Comatose, responding only to noxious stimuli; prolonged recovery period marked by alternating sleep and waking illusions, hallucinations, and clinical features of low dose state; amnesia for period of coma and prolonged recovery phase
Respirations			
Rate	16-24 (+)	16-24 (+)	18-28 (+)
Pattern	Normal	Normal or Cheyne-Stokes	Normal or Cheyne-Stokes (adult); apnea (child)
Circulation			
Blood pressure	135-160 / 80-100 (+)	135-160 / 80-100 (+)	120-200 / 60-110
Pulse	100-140 (+)	100-140 (+)	80-100 (+)
Pupils			
Size	Mid-position	Mid-position	Variable
Light reflex	Normal	Normal or sluggish	Normal or sluggish
Occular movements			
Eyelid position	Open/ptosis	Ptosis/closed	Closed
Nystagmus	Horizontal and vertical on testing	Horizontal and/or vertical at rest	Horizontal and/or vertical at rest
Motor function	Ataxia (sensory); catatonic rigidity—catalepsy, facial grimacing; deep tendon reflexes (DTR's)—increased	Purposeless movements, repetitive; myoclonus (shivering) —trunk, extremities; clonic jerking extremities; muscle rigidity on stimulation; facial grimacing; deep tendon reflexes (DTR's)—increased	Purposeless movements, muscle rigidity, opisthotonic posturing (child), generalized seizure activity, deep tendon reflexes (DTR's)—increased
Sensory function	Analgesia (pin prick)	.....	.....
Autonomic function	Vomiting (central)	Vomiting (central), hypersalivation	Vomiting (central), hypersalivation

response to pin prick is observed. Most of these patients were seen at rock music events and were able to return with friends to their seats after an hour, although mild ataxia was still evident.

The moderate dose state is marked by coma or stupor in which the eyes remain open associated with the presence of hypertension and the absence of respiratory depression. The pupils are mid-position and reactive to light. Nystagmus at rest, repetitive motor movements, myoclonus (shivering) and muscle rigidity on stimulation are characteristic findings. Frequently vomiting and hypersalivation are part of the picture. Most patients are communicative and ambulatory within 30 minutes to an hour, although they manifest all the signs and symptoms of the low dose state on awakening. One to two hours of observation are required from the time of admission until the patient returns with friends to the auditorium or stadium.

The patient who has taken orally a high dose of phencyclidine either accidentally or as a suicide attempt usually presents at the emergency room. The two children included in this series presented with apnea, although in the adult patients where information is available respirations were normal

and the blood pressure was normal or high. While pupil size varied, the pupillary light reflex was intact. Opisthotonic posturing was seen in one child over a six hour period, and generalized seizure activity has been observed in adult patients. Nystagmus at rest, vomiting and hypersalivation are, again, seen during the comatose period. The most characteristic feature of high dose oral ingestion is the prolonged recovery phase, marked by alternating periods of sleep and waking, misperceptions, disorientation, hallucinatory phenomena and the clinical picture of the low dose state. Patients have been comatose for periods of up to 12 hours and have required several days for recovery to normal.

Differential Diagnosis

The low dose state is frequently interpreted as secondary to an unknown psychedelic drug. The absence of mydriasis and the presence of gross ataxia and horizontal and vertical nystagmus are diagnostic of a phencyclidine intoxication.

The moderate dose state may be interpreted, initially, as a sedative-hypnotic overdose. However, the presence of hypertension and hyperreflexia (deep tendon reflexes or DTR's) and the absence of prominent respiratory depression differentiate the phencyclidine intoxicated state from sedative-hypnotic overdose.

Cases involving ingestion of high doses which present as undiagnosed coma may be difficult to differentiate from other causes. Again if hypertension is evident and there is no significant depression of respiration, sedative-hypnotic overdose can be ruled out. If, in addition, opisthotonic posturing is present in a child or seizure activity in an adult, a phencyclidine intoxication should be suspected. If a patient is in status epilepticus or in a postictal state, the underlying cause may be difficult to surmise. The characteristic prolonged recovery phase is diagnostic of phencyclidine intoxication.

Management, Treatment

The key to management of the low dose acute intoxicated state is sensory isolation with observation at a distance. Exacerbation of clinical symptoms is seen even with minimal verbal or physical stimulation. The patient should be placed on a cushioned surface of the floor in a quiet room with a monitor present. Protection from self-harm may also be necessary. Most patients are able to be released to family or friends within one hour.

In a patient who presents with the moderate dose state, respiratory status and blood pressure should be monitored, with close observation for clonic movements or muscle rigidity which usually precede seizure activity. Again, sensory stimulation should be controlled and minimized. On recovery from the short period of coma or stupor, the patient will require continued sensory isolation and protection from self-harm for approximately one hour.

If seizure activity does intercede, judicious intravenous administration of diazepam (Valium®) in 2 to 3 mg increments is indicated. Respirations should be closely monitored postadministration.

The general principles of management of coma would apply to high dose acute intoxication with phencyclidine. Closely monitoring respirations and blood pressure, and observing the patient for seizure activity or its prodromata would be indicated. Endotracheal intubation may be difficult and may precipitate laryngeal spasm. Gastric lavage is indicated in view of the large quantities of phencyclidine which have been recovered from the gastric contents in fatal cases.

Diazepam carefully administered in increments of 2 to 3 mg intravenously with postadministration observation of respirations is indicated in the event of generalized seizure activity. Diazoxide was reported to be effective in lowering blood pressure during a hypertensive crisis thought to be secondary to phencyclidine.[10]

The patient may remain comatose for a period of 12 hours or more. The principles of sensory isolation and protection from self-harm apply to the prolonged recovery period which may last several days and require admission to a psychiatric unit.

Fatalities

Fifteen deaths associated with phencyclidine, and previously unreported, occurred in California between 1970 and 1975. Five of these deaths occurred during the period January 1974 to July 1975. In all cases analysis of body fluids for toxicology showed the presence of phencyclidine and the absence of any other chemical agent. Most of these deaths appear to represent accidents or suicides involving a pharmacological overdose. In some cases, however, the levels of phencyclidine in the blood and urine and the circumstances of

the death suggest that death resulted from the behavioral toxicity of phencyclidine.

In the cases with high blood and urine levels, the associated presence of up to 185 mg of phencyclidine in the gastric contents points to an oral route of self-administration. In one case bloody fluid was noted in the mouth and nose which may have resulted from seizure activity. It is still unclear whether oral doses in the range of 150 to 200 mg or more, which were estimated to be involved in these cases, produce primary respiratory depression. Generalized seizure activity with postictal depression or hypoxia may be the precipitating factor in the death of these persons.

Interviews with chronic, daily users of phencyclidine do not support the idea that tolerance develops to the behavioral effects of this agent. Behavioral toxicity is consistent with the lower blood and urine levels found in four cases where the immediate cause of death was asphyxiation on drowning.

Chronic users report that friends have died while intoxicated by drowning, automobile accidents and fire. Gross ataxia, catatonic rigidity, misperception or analgesia may interfere with a person's ability to drive, swim, flee from a fire or sense imminent danger.

Discussion

The central question of the occurrence of primary respiratory depression in fatal high dose phencyclidine ingestions in adults remains unanswered. Blood levels in fatal cases have been comparable to the level reported in one patient who presented with status epilepticus (0.70 mg per 100 ml)[9] and the level in the single high dose case seen by the authors (0.37 mg per 100 ml). The former patient died four days after admission with autopsy evidence of severe anoxic encephalopathy and indications of progressive hepatic and renal failure. In the latter case no phencyclidine was detectable in the blood 7½ hours after admission, although the patient remained comatose with no significant change in respiratory function or seizure activity for 10 hours.

In a third case, where blood levels were not obtained, the patient also presented in status epilepticus. The 13 hour period of coma was marked by intermittent, generalized seizure activity with respiratory depression evident only after reiterative seizures. The information available is incomplete and the relationship between blood levels, respiratory depression and seizure activity has yet to be documented with clinical findings in cases involving potentially lethal doses of the drug.

Eastman and Cohen have recently reported a case involving a 13-year-old boy in which a hypertensive crisis was followed by an intracerebral hemorrhage and death.[10] There was no autopsy evidence of cerebral hemorrhage or hypertensive encephalopathy in the fatalities summarized.

Potentiation of the stimulant or depressant effects of phencyclidine in humans by other chemical agents is also an open question. While we have no familiarity with the intensity or spectrum of effects seen when phencyclidine is administered in comparable high doses, this becomes a critical question when central nervous system depressants are administered to control seizure activity. Judicious use of these agents would appear to be indicated.

It is not clear whether symptomatic improvement consistently follows the use of the phenothiazines. In several cases, however, significant hypotension has resulted from the administration of therapeutic dosages of the phenothiazines.

By 1964 more than 1,000 patients had received phencyclidine as an investigational drug and no evidence of acute cellular toxicity was reported.[11]

Conclusion

In contrast to its pronounced behavioral and central nervous system toxicity, phencyclidine parades as a "mild" psychedelic drug on the street. It has become one of the most frequently used main ingredients of street drug preparations. Further investigation of the cellular toxicity and neuropsychological dysfunction associated with chronic daily use of phencyclidine is indicated.

REFERENCES

1. Radcliff BE: Personal communication
2. Reynolds P: Personal communication
3. Chen G, Ensor C, Russell D, et al: The pharmacology of 1-(1-phenylcyclohexyl) piperidine HCL. J Pharmacol Exp Ther 127:241-250, May 1959
4. Greifenstein FE, Yoshitake J, DeVault M, et al: A study of a 1-aryl cyclo hexyl amine for anesthesia. Anesth Analg 37:283-294, Sep-Oct 1958
5. Liden CB, Lovejoy FH Jr, Costello CE: Phencyclidine (Sernylan) poisoning. J Pediatr 83:844-845, Nov 1973
6. Stein JI: Phencyclidine induced psychosis—The need to avoid unnecessary sensory influx. Military Med 138:590-591, Sep 1973
7. Highland General Hospital, Oakland, California: Personal communication
8. Davis W, Ezekiel G: Personal communication
9. Kessler GF Jr, Demers LM, Berlin C, et al: Phencyclidine and fatal status epilepticus. N Engl J Med 291:979, Oct 1974
10. Eastman JW, Cohen SN: Hypertensive crisis and death associated with phencyclidine poisoning. JAMA 231:1270-1271, Mar 24, 1975
11. Domino EF: Neurobiology of phencyclidine (Sernyl), a drug with an unusual spectrum of pharmacological activity. Int Rev Neurobiol 6:303-347, 1964

Refer to: Greenfield S, Anderson H, Winickoff RN, et al: Nurse-protocol management of low back pain—Outcomes, patient satisfaction and efficiency of primary care. West J Med 123:350-359, Nov 1975

Nurse-Protocol Management of Low Back Pain

Outcomes, Patient Satisfaction and Efficiency of Primary Care

SHELDON GREENFIELD, MD and HJALMAR ANDERSON, MD, *Los Angeles;* RICHARD N. WINICKOFF, MD, *Boston;* ANNABELLE MORGAN, MS, *Los Angeles;* and ANTHONY L. KOMAROFF, MD, *Boston*

To test the validity of a nurse-administered protocol for low back pain, a prospective trial of 419 patients was undertaken in a walk-in clinic. In all, 222 patients were randomly allocated to a "nurse-protocol group" in which they were evaluated by one of five nurses using the protocol; the nurses independently managed 53 percent of the patients and referred to a physician patients with potentially complex conditions. In addition, 197 patients in a randomly allocated control group were managed by one of 32 physicians. Care in the experimental and control groups was compared by follow-up telephone contact and by a four-month chart review. There was no significant difference in symptomatic relief or the development of serious disease in the two groups. Nurse-protocol patients expressed greater satisfaction with the care they had received; patient satisfaction correlated positively with symptom relief. In over 95 percent of the patients, there were noncomplex, nonserious, nonchronic conditions as the cause of back pain. We conclude that nurse-protocol management of this generally benign condition in a primary care setting is both effective and efficient.

From the Departments of Medicine and Preventive Medicine, University of California, Los Angeles, School of Medicine; the Ambulatory Care Project of the Department of Medicine, Beth Israel Hospital, Harvard Medical School, Boston, and the Massachusetts Institute of Technology, Lincoln Laboratory, Lexington; and the Southern California Permanente Medical Group.

This work was performed pursuant to Contract HSM 110-73-335 with the Bureau of Health Services Research and Evaluation, Health Resources Administration, Public Health Service, Department of Health, Education and Welfare.

Presented in part at the American Federation of Clinical Research National Meeting, Atlantic City, New Jersey, May 5, 1974.

Submitted March 17, 1975.

Reprint requests to: Sheldon Greenfield, MD, Room 73-274, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

PROTOCOLS (also called clinical algorithms) for common problems have been described in several recent reports.[1-7] Protocols have been used to train, guide and audit the performance of "new health practitioners"—nurses, nurse-practitioners and physician assistants. Studies of protocol-assisted management of such acute minor illnesses as upper respiratory infections[2] and urinary tract and vaginal infections[1] and of return visit management of chronic diseases[3] have indicated that practitioners other than physicians can help deliver safe, effective and efficient medical care.

We here report on the development and validation of a protocol for the complaint of low back pain. This is a frequent complaint in primary care practice and was the fourth most common complaint among adults with acute symptoms in a recent survey conducted by our group.[8] In contrast to common respiratory, urinary and vaginal infections, the management of low back pain may involve more important psychological aspects as well as more serious, complex disease. Low back pain, therefore, poses a challenge to the protocol approach, and to management by new health practitioners.

The protocol was used by a group of nurses in a prospective randomized controlled trial in which several hypotheses were tested:

- The complaint of low back pain in a primary care practice almost always indicates injury to muscles, ligaments or discs of the low back, with or without dorsal root compression; only infrequently is it due to other pathology, and rarely is it due to serious pathology.
- A system in which nurses using the low back pain protocol manage many patients without a physician examining those patients, and refer other patients to physicians, can be as medically safe and effective as a system in which only physicians manage patients, and can help physicians make more efficient use of their time.
- With a complaint which has as important a psychosocial component and as few objective criteria of improvement as low back pain, patient satisfaction with care correlates with symptomatic relief.

Methods

Description of the Protocol

The Low Back Pain Protocol was designed to provide a logical and medically sound approach to the evaluation of low back pain in adults. The protocol directs the protocol user (in this case, a nurse) to collect relevant data (history and findings on physical examination) and then guides the user through a sequence of decisions leading to an appropriate action—for example, diagnosis, therapy and disposition. The protocol itself is a single page form which combines a checklist for recording clinical data with a format that displays the logic of medical decisions necessary both in directing data gathering and in making management decisions appropriate to the particular patient (Figure 1). The medical judgments in the protocol were subjected to peer and consultant review. This kind of protocol, and the stages in its development, have been described elsewhere.[3,9-11]

Figure 2 outlines the major logic pathways through the protocol. The protocol supports the person using it in the independent management of the syndrome of low back strain: an injury to the muscles, ligament *or* discs of the lumbar spine. How often low back strain is actually due to disc damage is unclear.[12] It is generally agreed that most cases of low back pain are due to disc injuries even when there are no overt root signs.[13-15] The protocol never leads to the explicit diagnosis of disc disease, a diagnosis we feel for medicolegal reasons should be made by a physican. Rather, the protocol states the problem as "low back strain" and adds the phrase "with possible root irritation" when history or physical examination justifies that addition.

If in a woman presenting with low back pain there are also symptoms of dysuria or urinary frequency, analysis of urine is ordered and any urinary tract infection found is managed according to the recommendations of a protocol for urinary tract infections.[1]

Under protocol guidance those patients with severe pain from probable disc disease or persistent pain that is not improving with adequate bed rest, such as might be caused by ankylosing spondylitis, metastatic tumor, osteoporosis and the like are referred to a physician. The protocol also is designed to refer to a physician those patients who may have low back pain of any other cause. Patients suspected of having a gastrointestinal, genitourinary, neurologic, traumatic or local infectious cause for the back pain are identified by certain historical and physical examination screening data. For example, to detect gastrointestinal disease, questions about diarrhea, constipation and rectal bleeding are asked. Fever is used as an index of possible osteomyelitis or other infectious

LOW BACK PAIN PROTOCOL© (11/74)

Unit #: Date:

Name:

Birthdate: Phone:

Protocol User:

yes no SUBJECTIVE

- Seen <4 wks ago for same problem
- A Improved

Duration of pain _____

- Any previous episodes
- Age ⩾60

- Located in central back
- Right side
- Left side
- Groin *Do urinalysis & culture*
- Abdomen
- Buttock (which side?____)
- Thigh (which side?____)
- Below knee (which side?____)

- Tried bed rest (3 hrs, firm mattress, on back or side)
- Some relief during bed rest

- Made worse by coughing/sneezing
- Numbness/paresthesias below waist
- Blow (direct trauma) to low back in past 3 months
- Diarrhea
- Constipation
- Rectal bleeding
- Fecal/urinary incontinence
- Trouble urinating in last 12 hrs
- Unable to walk

- Dysuria *Do urinalysis & culture*
- Urinary frequency *Do urinalysis & culture*
- Male
- Urinalysis ordered
- Urethral discharge

OBJECTIVE

- A Pt appears in severe pain
- Temperature ⩾100 _____

- Normal heel walking
- Normal toe walking

- Abdominal pain by Hx
- Abdominal tenderness by Px

- Unilateral CVA tenderness *Do urinalysis and culture*
- Tenderness in back

right left

- Sciatic notch exam normal
- Straight leg raising normal
- Big toe elevation normal
- Sensation in foot normal

- Knee jerk
- Ankle jerk

- Knee jerks about equal
- Ankle jerks about equal

PLAN

- STOP Any reds *Consult MD*
- STOP Will consult MD for other reasons

- Return visit
- STOP STOP Signs better *Advance Rx* *Consult MD*

- Urinalysis ordered *Do UTI protocol, return*
- Dx of UTI *Dx Low Back Strain* *Rx Bed Rest*

- Any grays *Dx Low Back Strain with possible root irritation* *Rx Bed Rest* *Return in 3 weeks*

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Copyright: The Beth Israel Hospital Association, Boston, and Massachusetts Institute of Technology, Cambridge, 1974 — HEW Contract No. HSM 110-73-335.

Figure 1.—Single page protocol form used in study.

cause of back pain. Patients who are over age 60 (older people having a much higher incidence of metastatic disease and other serious causes of low back pain) and patients with pain in the abdomen, fecal or urinary incontinence, urinary retention, inability to walk, urethral discharge or severe pain are all referred to a physician. The protocol is not applicable to patients who have suffered traumatic injury to the back from a direct blow, auto accident or fall. Those patients are at risk for posterior arch vertebral fractures and dislocations which can potentially cause spinal cord damage, and should be seen immediately by a physician. The protocol also does not apply to patients with pain in the neck, arm or shoulders, and patients with symptoms or a viral respiratory infection, because simple low back strain is less likely in these groups.

The protocol does not recommend ordering lumbar spine x-ray studies; we believe that they do not help in the management of uncomplicated low back strain, and that most serious causes of low back pain will be identified by the screening, historical and physical examination data. Those few patients with serious but nonacute disease, such as metastatic cancer to the lumbar vertebrae or osteoporosis, are expected to return in a short period after not responding to symptomatic treatment, if they have not been identified at the initial visit.

Patients with low back strain are placed at bed rest for a period of up to seven days and are given prescription for analgesics or diazepam or both at the discretion of the practitioner. Patients who also have suspected dorsal root irritation are given similar medications, and told to return for reevaluation in three weeks. All patients who do not respond to treatment are told to return. The complete protocol and a detailed discussion of its medical content and logic are presented elsewhere.[16]

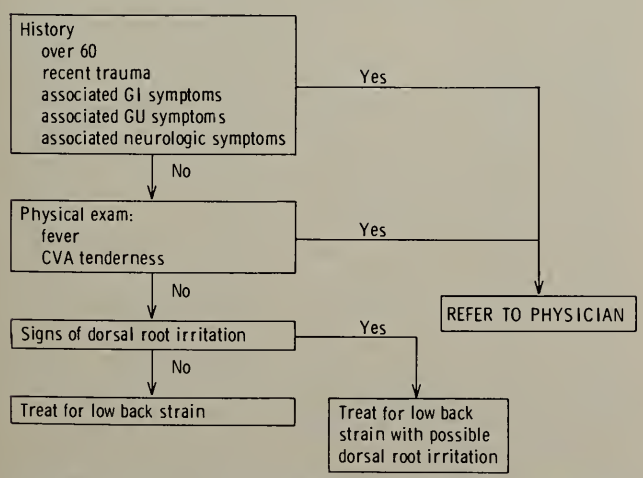
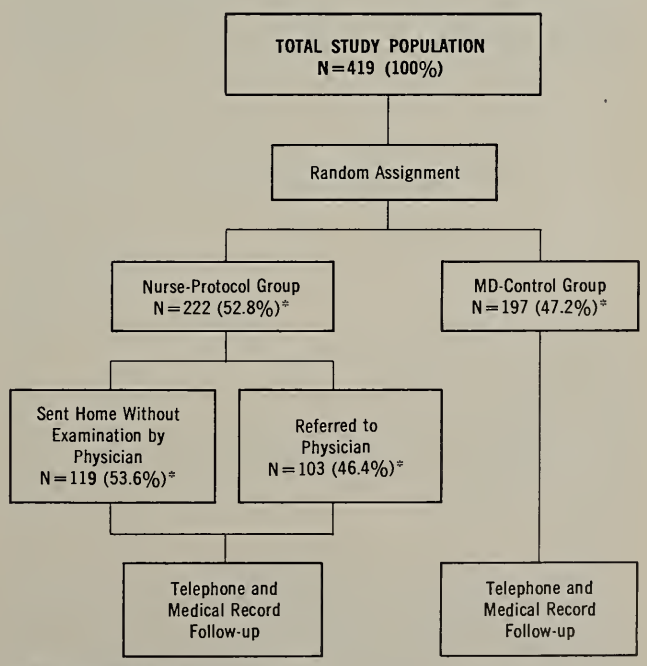


Figure 2.—Major pathways through the backache protocol.

Study Design

The study design is represented in Figure 3. The study was conducted in the Walk-In Clinic of the Kaiser Permanente facility in Inglewood, California, between July 1973 and May 1974. Patients who presented to the clinic with the complaint of low back pain were randomly allocated into one of two groups. One group of patients was first evaluated by one of five nurses using a protocol. If the protocol recommended that the patient be referred by the nurse to a physician that day, a physician supervisor saw the patient and his management plan was followed. If the protocol recommended that the patient be sent home with specific therapy, the nurse's findings, as recorded on the protocol, were reviewed by the physician supervisor and, if acceptable, the protocol management plan was followed without the physician examining the patient. This group of patients are hereafter referred to as the *nurse-protocol group*. A second group of patients was randomly assigned to be seen only by one of 32 physicians working in the clinic that day. These patients are hereafter referred to as the *MD-control group*. The physicians in this group were aware that a study was in progress; however, there was no formal introduction of the protocol or its



*Percent of respective subgroup

Figure 3.—Illustration of study design.

TABLE 1.—*Age and Sex Distribution of Patients in Nurse-Protocol and MD-Control Groups*

	Nurse-Protocol Group		MD-Control Group	
Age	*Number*	*Percent*	*Number*	*Percent*
10-19	15	6.8	7	3.6
20-29	53	23.9	44	22.3
30-39	60	27.1	74	37.6
40-49	48	21.3	54	27.4
50-59	32	14.5	15	7.6
60-69	11	5.0	3	1.5
70+	3	1.4	0	0.0
TOTAL	222	100.0	197	100.0
Sex				
Male	107	48.0	88	44.7
Female	115	52.0	109	55.3
TOTAL	222	100.0	197	100.0

logic to these physicians. To our knowledge, none of the physicians inquired about the logic used, and none acquired a copy of the protocol.

All patients in both groups were followed-up by a telephone interview within five weeks of the initial clinic visit (mean number of days later was 27 for the nurse-protocol group and 33 for the MD-control group). The interviewer was a research assistant who used a questionnaire designed to assess the patient's satisfaction with the care received, as well as to determine whether the patient had improved symptomatically.

In addition to the telephone follow-up, the medical records of all patients in both groups were reviewed four months after the clinic visit to ascertain whether serious sequelae had developed. Roemer showed that only 7.2 percent of admissions to hospital of patients enrolled in the Kaiser plan occurred in other institutions.[17] It therefore seemed that this record review would be adequate to assess the development of serious problems. All records were done by one of us (S.G.).

Results

Characteristics of Patients and Providers

Of the 592 patients who were admitted to the study, 419 (70.1 percent) completed the study. A similar proportion (no statistically significant difference) of patients in the nurse-protocol group (25.8 percent) and in the MD-control group (32.8 percent) failed to complete the study for two major reasons: some patients who had been assigned to the study on a random basis by the triage clerk were found not to have low back pain; other patients could not be followed-up despite repeated telephone calls. The final study population comprised 419 patients, 222 (52.8 percent) in the nurse-protocol group and 197 (47.2 percent) in the MD-control group.

The age and sex distribution of the patients in both groups is shown in Table 1. Most patients in both groups were between the ages of 31 and 59. There were no statistically significant differences between the groups. A more detailed demographic description of the patient population is found elsewhere.[17]

The mean age of the 32 physicians was 36 years old. Of the 32 physicians, 17 were internists; the rest were general practitioners. All five of the nurses were registered nurses (RN)—none had formal nurse-practitioner training; four

TABLE 2.—*Distribution of Initial and Final Diagnoses in Nurse-Protocol and MD-Control Groups*

	Nurse-Protocol				MD-Control			
	Initial Diagnosis		Final Diagnosis		Initial Diagnosis		Final Diagnosis	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Low back strain*	187	84.2†	208	93.7	175	88.8†	174	88.3
Urinary tract infection	6	2.7‡	7	3.2	9	4.6‡	10	5.1
Pelvic source§	0	0.0	0	0.0	4	2.0	4	2.0
Gastrointestinal source§	0	0.0	0	0.0	1	0.5	1	0.5
Viral syndrome	5	2.2	5	2.2	5	2.5	5	2.5
Viral syndrome and urinary tract infection	0	0.0	0	0.0	1	0.5	1	0.5
Other¶	24	10.8‖	2	0.9	2	1.0**	2	1.0
TOTAL	222	100.0	222	100.0	197	100.0	197	100.0

*With or without dorsal root irritation.
†One patient in each group was initially misdiagnosed as having muscle strain; urinary tract infections discovered on return visit.
‡These patients had initial presumptive urinary tract infections (UTI) according to urinalysis findings of ≥10 leukocytes on high power field. One of the protocol patients had a chronic UTI, due to urinary tract anomaly.
§Nonspecific, possible pelvic inflammatory disease, gastroenteritis.
¶Possible fracture, contusion, osteoarthritis, suspect serious disease.
‖In one patient there was a documented ureteral stone and in one patient there was continuing pain, possibly due to contusion; all others turned out to have muscle strain on final evaluation.
**In one patient, severe degenerative changes were shown in lumbar spine x-ray studies.

TABLE 3.—*Patient Satisfaction Assessment*

Question	Positive Response: Nurse–Protocol (N=222 Respondents) Percent	Positive Response: MD-Control (N=197 Respondents) Percent	P
Did you seek help elsewhere for your problem after your visit?	19.4	23.9	NS
"I was satisfied with my contact with nurse/MD"	89.2	78.2	<.004
"The nurse/MD encouraged me to talk about other health problems"	78.4	55.8	<.0001
"The medical care I received for my backache was better than my usual visits for a health problem"	45.1	33.5	<.02
"The nurse/MD showed concern for me"	96.9	83.8	<.00001
"I feel the nurse/MD understood what was bothering me"	88.7	82.7	NS
"On the basis of what the nurse/MD said to me, I feel that I understand my present medical condition"	72.1	65.0	NS
"The nurse/MD did spend enough time with me"	96.4	80.2	<.0001
"I would prefer to see the same caregiver the next time I come to Kaiser"	96.4	83.8	<.0001

P = level of significance.

TABLE 4.—*Relation of Symptom Relief to Practitioner Preference*

	Back Pain Relieved		Back Pain Not Relieved		Totals	
	Number	Percent*	Number	Percent*	Number	Percent*
Prefer same practitioner	259	61.8	86	20.5	345	82.3
Not prefer same practitioner	38	9.1	36	8.6	74	17.7
TOTALS	297	70.9	122	29.1	419	100.0

*Percent of total study group.

had taken in-house lecture courses for nurse-practitioners, but their only prior clinical experience was in managing upper respiratory infections and in screening histories and physical examinations. Preparation for use of this protocol consisted of an orienting lecture, several observations of a physician using the protocol and a dozen or so uses of the protocol by the nurse in the presence of a physician. None of the results of this study showed any significant differences in performance among the five nurses or among the 32 physicians.

Diagnosis Distribution

The distribution of both initial and final diagnoses for both groups is shown in Table 2. The *initial* diagnoses in the nurse-protocol group were made by either the nurse alone, guided by the protocol, or by the supervising physician to whom some of the patients were referred. The *final* diagnoses were established by medical record review four months following the initial visit. Of the 419 patients, 91 percent had low back strain with or without mild dorsal root compression on final diagnosis; all but four patients had noncomplex, nonserious conditions.

There were no statistically significant differences between the nurse-protocol and MD-control groups in the distribution of either initial or final diagnoses, except for the initial diagnosis of "other" ($p<.01$).

Safety

Medical record review four months following the clinic visit showed that in none of the patients managed by the nurses alone had any serious sequelae developed. Three patients with more complex conditions—one with a ureteral stone documented by intravenous pyelogram, one with a urinary tract anatomic anomaly and one with possible contusion—were detected (not diagnosed) by elements of the protocol history and physical examination; they were appropriately referred to a physician.

A total of 48 of the nurse-protocol group patients and 32 of the MD-control group patients with the initial diagnosis of low back strain returned to the clinic over the subsequent four months for recurrences of low back pain. Physicians examined all of these patients and again diagnosed low back strain.

One patient from each group with the initial diagnosis of low back strain returned within ten days with symptoms of urinary tract infection, confirmed by culture. It is reasonable to assume

that this infection had been the cause of the low back pain, but had been overlooked on their initial visit.

Of those patients in whom the initial presumptive diagnosis was urinary tract infection, all six of the cases in the nurse-protocol group were confirmed by culture. In only four of the nine cases in the MD-control group did cultures give positive findings; in the remaining five, urethral syndrome (urethritis) or low back strain may have been present.

Symptom Relief and Satisfaction

Results of telephone follow-up showed that symptoms were totally resolved or definitely improved in 162 (73.0 percent) of the 222 nurse-protocol patients and in 135 (68.5 percent) of the 197 MD-control group patients. The difference is not statistically significant. To investigate whether the level of symptom relief in the nurse-protocol group was due to those patients who also saw a supervising physician, we separately analyzed the responses in patients who only saw a nurse. Symptom relief occurred in 94 of the 119 nurse-only patients (79.0 percent), a higher proportion than in the total nurse-protocol group.

In the telephone follow-up, nine questions were asked designed to elicit evidence of patient satisfaction with the care they had received for the episode of low back pain. Table 3 summarizes these findings. It can be seen that patients in the nurse-protocol group were in all cases as satisfied as patients in the MD-control group. Responses to six of the questions indicate a statistically significant superiority in the degree of satisfaction among the nurse-protocol patient group. Again, as with symptom relief, the high degree of satisfaction in the nurse-protocol group patients was not caused by patients who were also seen by supervising physicians. Of the 119 nurse-only patients, 16 (13.4 percent) said that they had sought help elsewhere. Similar responses were found for the other questions.

Relation of Symptom Relief and Patient Satisfaction

Because relief of pain is a subjective outcome, the relief of a patient's pain might be correlated with the patient's satisfaction with his or her care. Table 4 shows the relationship between this index of satisfaction and symptom relief ($p<.01$). This same relationship held when other questions reflecting patient satisfaction were compared to symptom relief.

Efficiency

In the nurse-protocol group, 53.6 percent of the patients were evaluated and begun on a program of therapy by the nurses, without further examination by a physician. No formal measurements were made of actual time spent by physicians and nurses with patients. The protocol recommended that patients with signs of root irritation return for care under explicit circumstances; therefore these scheduled return visits could have affected the efficiency of care for an episode of low back pain. In the nurse-protocol group, 27.1 percent of the patients returned within the following three months for care of back pain, compared with 18.3 percent of the MD-control patients. The difference is not statistically significant.

Of the 103 patients in the nurse-protocol group referred by nurses to a physician, in 69 there was a final diagnosis of low back strain, with or without dorsal root irritation. These patients had been referred to a physician for symptoms suggesting possibly more complex disease, yet they were diagnosed by the physician as having only low back strain—a condition which the protocol was designed to manage. Therefore the conservatism of the protocol in seeking to assure medical safety reduced efficiency.

Results of X-Ray Studies

Analysis of radiographic examinations of the lumbar spine indicated that 21 x-ray studies were ordered in the nurse-protocol system and 36 in the MD-control group ($p<.01$). Since the protocol did not recommend ordering any laboratory tests, all tests in the nurse-protocol group were ordered by the physician to whom some of the patients were referred. Of the 57 x-ray studies ordered, only one clearly altered the clinical impression and management of the patient. In this patient, severe degenerative joint disease of the spine was present. The remainder of the x-ray studies showed mild to moderate degenerative changes which were not considered to be causes of the presenting complaint.

Discussion

Before discussing the study results, certain general limitations of the study should be acknowledged. The study was conducted in the walk-in clinic of one particular setting, a large prepaid group practice, and involved a particular group of nurses, physicians and patients. One

must therefore be cautious in generalizing this experience to other settings. Also, as with any recently implemented innovation undergoing study, there is always the possibility that the initial enthusiasm of the nurses with their new role and the process of studying the system may have introduced positive biases.

Typical Causes of Low Back Pain Seen in a Primary Care Setting

In developing the low back pain protocol we proceeded from the following hypothesis: patients presenting with the complaint of low back pain in a primary care practice do not typically have the complex and serious underlying diseases often emphasized in discussions of low back pain written by orthopedists and other specialists. The distribution of diagnoses in these 419 patients shows that, in a primary care setting, a very large percentage of patients will have benign, noncomplex, nonemergency conditions. Low back strain with or without dorsal root irritation was present in 91 percent of the patients. In another 5 percent, there was either urinary tract infection, possibly mild pelvic inflammatory disease, or mild gastroenteritis. In four patients (1 percent), there were potentially chronic and complex conditions which needed continuing careful medical attention: ureteral stone, urinary tract anomaly, possible contusion, severe degenerative joint disease. In these 419 patients, there were no neoplastic or serious infectious diseases causing the back pain.

In a discussion in *Sign and Symptoms,*[18] Freyberg describes many possible causes of low back pain. The *major* categories, not all-inclusive, are: fractures, dislocations, spondylolisthesis, osteoporosis, infections, metastatic carcinoma, multiple myeloma, ankylosing spondylitis, osteoarthritis, intervertebral disc disease, back muscle strain, muscle spasm, myositis, collagen disease, fibrositis, trauma, postural defects, gastrointestinal sources, obstructive uropathies, prostate inflammation, pelvic disorders in females and systemic infections. Given this array of possible causes, how far does a practitioner go in the workup of a patient presenting with low back pain?

Clearly, the practitioner cannot carry out every conceivable diagnostic maneuver or laboratory test for every conceivable cause of low back pain on every patient. Besides the practical limitations of such an approach, it is unlikely that this would be in the patient's best interest. In deciding on an appropriate workup, the clinician must consider the frequency of various causes of low back pain.[19] Second, he must be aware of these possible causes of low back pain which, however rare, are too potentially serious to be overlooked; the protocol logic attempts to identify clinical findings suggesting such serious illness, and to refer such patients to the physician. Then the clinician must decide which data must be collected in order to recognize both the frequent and the infrequent but serious clinical entities. The Low Back Pain Protocol formalizes this kind of thinking, based on a careful review of the medical literature and consultation with a number of academic and practicing physicians.

Quality of Care

The study supports the hypothesis that safe and effective care could be delivered by the system in which nurses using the protocol managed many patients without a physician examining those patients, while referring patients in other more complex situations to physicians. This nurse-protocol system was compared to a system in which only physicians managed a group of patients presenting with low back pain. This latter system was chosen as a control for two reasons: if nurses or other providers of care are to exercise expanded responsibilities for the management of clinical problems such as low back pain, it should be shown that the quality of care does not suffer in comparison with the care that physicians render; second, the medical literature does not contain outcome standards against which success in management of low back pain as a *symptom* can be compared.

The nurse-protocol and MD-control group patients were randomly allocated, and had comparable age, sex and clinical characteristics. Both groups were followed prospectively according to specific predetermined criteria. Safety, effectiveness and efficiency of care between the two groups could therefore be compared validly.

Safety of care was determined by medical record review four months after the clinic visit. We looked for the development of serious illness which might initially have been misdiagnosed as benign low back strain. In none of the patients managed by the nurses alone were any serious sequelae noted at the four month follow-up. Three patients with more complex conditions—one with a ureteral stone, one with a urinary tract anomaly and one with possible contusion—were detected by elements of the protocol history and

physical examination; they were appropriately referred to a physician. Therefore, the protocol appears to have detected all of the potentially serious and complex conditions occurring in this group of patients. It is possible, of course, that serious illness initially misdiagnosed as low back strain may have become manifest after the four month follow-up.

In one patient in the nurse-protocol group, and in one in the MD-control group, there may have been an initial misdiagnosis of low back strain when in fact a urinary infection was present.

Conversely, in four of the nine patients in the MD-control group who were given antibiotics for the presumptive diagnosis of urinary tract infection, findings were negative on urine cultures. However, in all six patients in the nurse-protocol group given antibiotics for this presumptive diagnosis, findings were positive on cultures.

Effectiveness of care was determined by measuring relief of symptoms and patient satisfaction through telephone follow-up of all patients in both groups approximately four weeks following the clinic visit. The symptoms had totally resolved or "definitely improved" in 73.0 percent of the nurse-protocol group patients and in 68.5 percent of the MD-control group patients.

The patients managed in the nurse-protocol group expressed significantly greater satisfaction with the care they had received in comparison with similar MD-control patients. The research assistant using the questionnaire during telephone follow-up was not a provider of care to the patient. Furthermore, the same questionnaire was applied to both randomly allocated groups of patients, and any bias which might have been introduced by the language of the questions should have been reflected equally in both groups.

We can only speculate as to why patient satisfaction and symptom relief within the nurse-protocol group was, in general, superior to the MD-control group. Guided by the protocol, the nurses did a systematic and thorough workup including careful examination for dorsal root signs; it was apparent from chart review that physicians recorded, in general, a less thorough examination. Although we did not take time measurements on multiple encounters, we estimated that the nurses spent approximately 15 to 20 minutes on an average encounter whereas the physicians spent about 10 minutes; the extra time may have been appreciated by the patients.

Although patient satisfaction and symptomatic outcome are often assumed to be related, these are the only data of which we are aware that show a significant relationship in a group of clinically similar patients. These data suggest that symptomatic relief may be, at least in part, a function of the satisfaction of the patient encounter. Therefore, satisfaction may be used to predict outcome. Clearly, patient satisfaction has a complicated relationship to outcome; many patients who expressed dissatisfaction with their care nevertheless experienced relief of symptoms. Conversely, many patients who were satisfied with their care continued to suffer and in some instances became worse. Further insights into the relationship between patient satisfaction and symptom relief await more refined and better validated measures of patient satisfaction.

Efficiency of Care

It was shown that 53 percent of the 222 nurse-protocol patients could be evaluated, diagnosed and treated entirely by nurses using the protocol, without a physician having to further examine the patient. This implies a significant saving of physician time, although precise measurements of physician time saved and nurse time spent were not made. Studies are currently underway to evaluate further the question of efficiency.

With respect to laboratory tests, analysis of lumbar spine x-ray studies showed cost saving without sacrifice of quality in the nurse-protocol system. In patients having the diagnosis of low back strain, x-ray studies of the lumbosacral spine were not made. There were no instances, in this group, in which an x-ray study should have been made, as determined by outcome. These data suggest that the protocol decision is sound in this regard and that many fewer x-ray studies than the physicians ordered need be done. It is difficult to attach a dollar amount to the difference in the number of x-ray studies ordered because we can not ascertain retrospectively the indications for ordering them in either group. However, it is estimated that the cost saving would be considerable.

REFERENCES

1. Greenfield S, Friedland G, Scifers S, et al: Protocol management of dysuria, urinary frequency, and vaginal discharge. Ann Intern Med 81:452, 1974

2. Greenfield S, Bragg FE, McCraith DL, et al: Upper-respiratory tract complaint protocol for physician-extenders. Arch Intern Med 133:294-299, Feb 1974

3. Komaroff AL, Black WL, Flatley M, et al: Protocols for physician assistants—Management of diabetes and hypertension. N Engl J Med 290:307-312, Feb 7, 1974

4. Sox HC, Sox CH, Tompkins RK: Training of physician's assistants by a clinical algorithm system. N Engl J Med 288: 818, 1973

5. Winickoff RN, Ronis A, Black WL, et al: Management of minor respiratory illnesses by nurses using a protocol. Clin Research 22:382A, 1974

6. Levy JC, Strong RM, Browne C: An integrated system for health supervision. Pediatr Clin North Am 21:291-305, May 1974

7. Charles G, Stimson DH, Maurier MD: Physician's assistants and clinical algorithms in health care delivery. Ann Intern Med 81:733, 1974

8. Quarterly Progress Report 11A: Ambulatory Care Project. Lexington, Massachusetts, Lincoln Laboratory, Massachusetts Institute of Technology and Beth Israel Hospital, August 1, 1974

9. Komaroff AL, Reiffen B, Sherman H: Problem-oriented protocols for physician-extenders, *In* Walker HK, Hurst W, Woody M (Eds): Applying the Problem-Oriented System. New York, Medcome, 1973

10. Sherman H, Komaroff AL, Reiffen B: Ambulatory care systems, *In* Driggs MF (Ed): Problem-Directed and Medical Information Systems. New York, Intercontinental Medical Book Corporation, 1973

11. Greenfield S: Protocols as analogs to standing orders, *In* Bullough B (Ed): The Law and the Expanding Nursing Role. New York, Appleton-Century-Crofts, Inc. (In Press)

12. Wilson PD, Levine DB: Low back pain and sciatica, *In* Hollander JL, McCarty (Eds): Arthritis. Philadelphia. Lea & Febiger, 1972

13. Key JA: Intervertebral disc lesions are most common causes of low back pain with or without sciatica. Ann Surg 121: 534, 1945

14. Burns BH, Young RH: Protrusion of intervertebral disc. Lancet 249:424, 1945

15. Williams PC: The Lumbosacral Spine. New York, McGraw Hill Book Co., 1965

16. Winickoff RN: Introduction to the low back pain protocol. Lexington, Massachusetts, Massachusetts Institute of Technology, Lincoln Laboratory and Beth Israel Hospital, 1974

17. Roemer MI, Hetherington RW, Hopkins CE: Services, expenditures, and attitudes under three types of plans, *In* Health Insurance Effects. Bureau of Public Health Economics, Research Series No. 16. School of Public Health, University of Michigan, 1972

18. Freyberg RH: Back pain, *In* MacBryde CM, Blacklow RS (Eds): Signs and Symptoms. Philadelphia, J. B. Lippincott Co., 1970, p 203

19. Schwartz WB, Gorry GA, Kassirer JP: Decision analysis and clinical judgment. Am J Med 55:459-472, Oct 1973

Neurological Complications of Cardiovascular Disease

There is no doubt that there is a specific relationship between central nervous system problems and the electrocardiogram (EKG). The exact mechanisms have not been determined. What is important, and something not documented in the literature, is that if you are faced with a patient who you think might have a primary disease in the heart (myocardial infarction) but also has a stroke, and you are really not sure how to tell the difference, a famous cardiologist whom I will name—Dr. Joseph K. Perloff, University of Pennsylvania—states that in his experience, a patient with a central nervous system problem never has Q waves on an EKG. The presence of Q waves would point the physician to look at the heart more than the head, in the face of acute cardiac changes.

—ROBERT JAY SCHWARTZMAN, MD. *Miami*
Extracted from *Audio-Digest Internal Medicine,* Vol. 22, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Cooperman LR, Seltzer RA, Reimer GW, et al: Xeromammography in the early detection of breast cancer—Community hospital experience and approach. West J Med 123:360-366, Nov 1975

Xeromammography in the Early Detection of Breast Cancer

Community Hospital Experience and Approach

LAWRENCE R. COOPERMAN, MD, RONALD A. SELTZER, MD, GEORGE W. REIMER, MD *and* STANFORD B. ROSSITER, MD, *Redwood City, California*

Community hospitals can do much in the general effort toward earlier detection of breast cancer. Using xeromammography in the department of general radiology of one community hospital, 21 cases of occult carcinoma were detected in 2,392 patients in a two year period. Patients were both symptomatic and asymptomatic. This percentage is comparable to results in previously published series of similar patient populations, and can be expected to be slightly higher than screening populations of totally asymptomatic patients. In 24 percent of cases of occult carcinoma there was axillary node involvement, compared with 42 percent axillary node involvement in cases of nonoccult carcinoma.

Early detection efforts are currently centered on improving thoroughness in physical examinations, stressing breast self-examination and identifying patients in high-risk categories. These, together with proper periodic use of mammograms, will yield the highest rate of early carcinoma detection until more sensitive biologic markers are developed.

PUBLIC AND MEDICAL INTEREST in all aspects of breast cancer is at an all-time high. Because of prevalence statistics, reports on early cancer detection given at medical meetings and widely disseminated in the media, and by the well publicized illnesses of Mrs. Ford and Mrs. Rockefeller, physicians today are confronted by increasingly informed and concerned patients, requesting examination and advice. The mass screening programs instituted as a demonstration project in 1973-74 by the American Cancer Society and National Cancer Institute have also excited public interest because results have shown success in early detection. Community hospitals and their physicians, outside of mass screening situations, are still at the forefront of patient care, however, and their

From the Department of Radiology, Sequoia Hospital, Redwood City, California.

Submitted April 18, 1975.

Reprint requests to: Lawrence R. Cooperman, MD, Department of Radiology Sequoia Hospital, Whipple and Alameda, Redwood City, CA 94062.

role in early breast cancer detection is the subject of this report.

In November 1972 we began the use of xeromammography,[1-7] preceded by an information campaign to our medical staff on its indications, usefulness and general applicability. Our hospital is a fairly typical community institution of 350 beds in the San Francisco Bay Area. Before this time we had been doing film mammography using a double film pack (Kodak® Industrial AA and M) without full clinical effectiveness. Our group of four general radiologists was able to quickly develop reasonable facility in xeromammographic interpretation, and our technicians after brief training were able to produce satisfactory images (overhead film technique, tungsten target). One of our members attended a training course at the Hutzel Hospital in Detroit, as recommended by the Xerox Corporation. Initial case load was about five to six patients daily, which has now risen to about ten to twelve a day.

Results of Xeromammography

In a 24-month period, xeromammography was carried out on 2,392 patients. Patients, referred for varying reasons, included both symptomatic and asymptomatic women, some with breast masses or pain, some desiring routine screening. Histologic proof was obtained in 298; in 97 of these cases malignancy was found. There were 22 false negative results of examinations, 56 false positive results and 21 cases of clinically occult cancer detected because of xeromammography. The results are tabulated in Table 1.

Our reports could be classified into one of four categories: (1) definite carcinoma; (2) suspicious for carcinoma; (3) probably benign but carcinoma cannot be excluded, biopsy or follow-up examination recommended, and (4) definitely benign. Although a definitive report is more desirable, this is frequently not possible (as in much of roentgenographic diagnosis) and many cases will fall into categories 2 or 3. This is an inevitable reflection of the state of the art as it has advanced to date, and leads into a discussion of the problem of false positive findings.

TABLE 1.—*Results of Xeromammography*

Total xeromammographic examinations	2,392
Total with histologic proof	298
Benign	201
Malignant	97
Clinically occult lesions detected	21
Number of these with negative axillary nodes	16
False negative interpretations	22
False positive interpretations	56

TABLE 2.—*Radiological and Clinical False Positive Findings—Benign Cases*

Negative clinically, positive xerogram	56
Positive clinically, positive xerogram	47
Positive clinically, negative xerogram	96
Radiological false positive rate	51%
Clinical false positive rate	72%

False Positive Findings

There were 56 patients in whom biopsy was carried out based only on xeromammography with benign histologic results. The number of false positive findings (Table 2) results from multiple factors. Many cases of carcinoma will show only as an area of asymmetry or ductal prominence (Figure 1), indistinguishable from benign disease (Figure 2). The scattered calcifications of sclerosing adenosis may be indistinguishable from those of carcinoma. It is often difficult to differentiate fibroadenomas, cysts and medullary carcinomas. However, since the stakes are high, and the usual morbidity from breast biopsy low, large numbers of false positive findings are acceptable. Clinical judgment, age, history, family history and findings on physical examination all must be correlated with the xerographic findings. During the same period, biopsies were done in 98 benign cases on clinical grounds alone, with negative mammo-

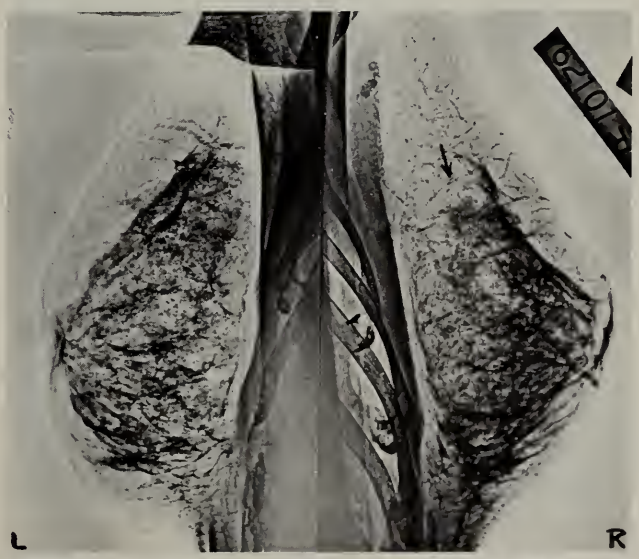


Figure 1.—Xerogram in a 47-year-old patient who thought she felt a mass in upper right breast which could not be confirmed on clinical examination. Dysplastic breasts with asymmetry in the upper portions are seen. A rounded area of increased density in the right breast (R) with adjacent areas of adenosis, was reported as suspicious for carcinoma. Infiltrating ductal carcinoma was diagnosed at surgical operation.

Figure 2.—Xerograms in a 70-year-old patient with mass palpable in upper outer right breast. Pronounced asymmetry in the upper part of breast was reported as suspicious for carcinoma on the right (**R**). At surgical operation mammary dysplasia was diagnosed.

Figure 3.—A 55-year-old patient with mass palpable in lower portion of left breast. Close-up of xerogram shows well circumscribed mass with halo of surrounding fat clearly circumscribing the lesion except for one area where smaller nodular density projects posteriorly. Aspiration was recommended, as well as biopsy if findings were not clearly benign. Fluid removed was cytologically benign, but cyst recurred in two weeks. Findings on biopsy then showed an 8 mm malignant lesion arising in the wall of the cyst.

graphic reports. Forty-seven benign biopsy specimens were obtained with both clinical and xeromammographic findings as suspicious. In cases of a well circumscribed mass in the middle or older age group, we recommend aspiration and cytologic examination of the fluid. If the appearance of the fluid is suspicious or the cyst recurs, biopsy is then immediately indicated. If there is any loss of continuity of sharp margination or local nodularity, suspicion of malignancy is immediately increased (Figure 3).

Specimen radiography is a necessary adjunct to biopsy and is done in cases where there are calcifications or a discrete mass to aid in determining if the lesion in question has been removed. Architecture change can also be evaluated by this method (Figure 6, Right). Lately we have placed needles in the breast preoperatively to aid in localization.[8]

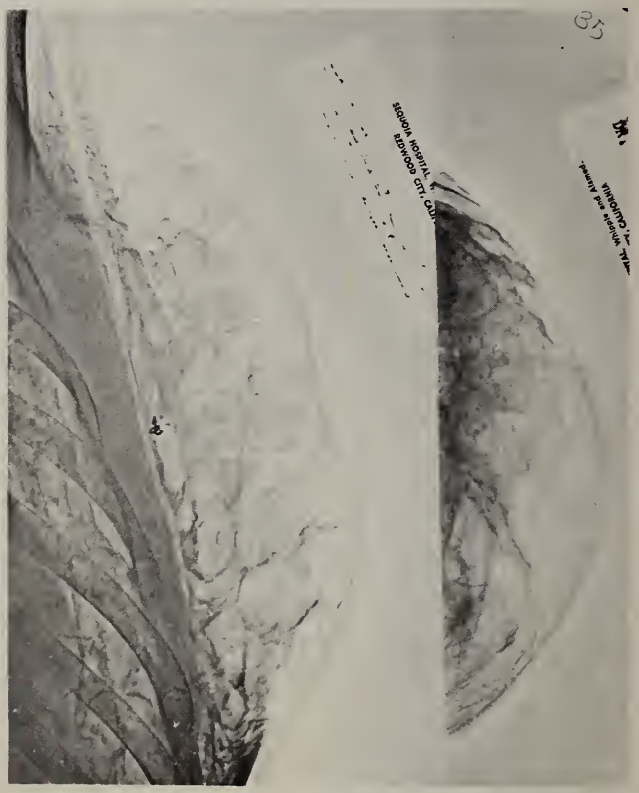


Figure 4.—A 51-year-old patient, with previous left mastectomy and previous right biopsy but with no previous mammogram. Right xeromammogram, lateral view (**left**) and craniocaudad view (**right**) show diffuse increase in density greatest in upper outer quadrant with no localized mass or stippled calcification. Coarse calcifications against chest wall were considered consistent with degenerated fibroadenoma. A mass was palpable in upper outer portion of the breast. Xeroradiographic report was no malignancy. Patient desired simple mastectomy because of anxiety over chronic masses. Infiltrating ductal carcinoma was found in lower outer quadrant three months after xeromammography.

False Negative Findings

There were 22 false negative cases (Table 3). In 12 patients, the presence of carcinoma could not be definitely determined even in retrospect. In some, certainly by "over-reading" one could argue for slight abnormality knowing the eventual site of carcinoma, but looking at the case as one would view one of the daily film load, the diagnosis could not be made. Furthermore, in four of these cases, there was a lag of from four to eight months between the mammogram and the surgical diagnosis. Mammography was not repeated immediately before biopsy and some changes may have become visible. In two patients, mastectomy had been carried out previously with no prior mammogram available for comparison, and the currently involved breast showed only what appeared to be dysplastic changes. Therefore asymmetry could not be determined (Figure 4). Previous mastectomy makes interpretation of less obvious malignant changes more difficult. Comparison with prior studies is quite helpful and *is a strong indication for xeromammography in all cases of breast carcinoma coming to surgical operation, to establish a baseline for future xeroradiographic examination of the opposite breast.*

TABLE 3.—*Findings in Examinations Giving False Negative Results*

Carcinoma not visible retrospectively	12
Asymmetry not appreciated	6
Calcifications missed (incomplete exam)	1
Architecture change missed	1
Carcinoma arising in cyst	1
Increased density and duct activity, follow-up previous opposite mastectomy	1

TABLE 4.—*Comparison with Other Series for Occult Cancer*

	Total xeromammograms	*Clinically occult*
Sequoia Hospital	2,392	21
Martin[6]	1,535	13
Frankl[10]	7,010	75
Frankl[11]	15,934	121

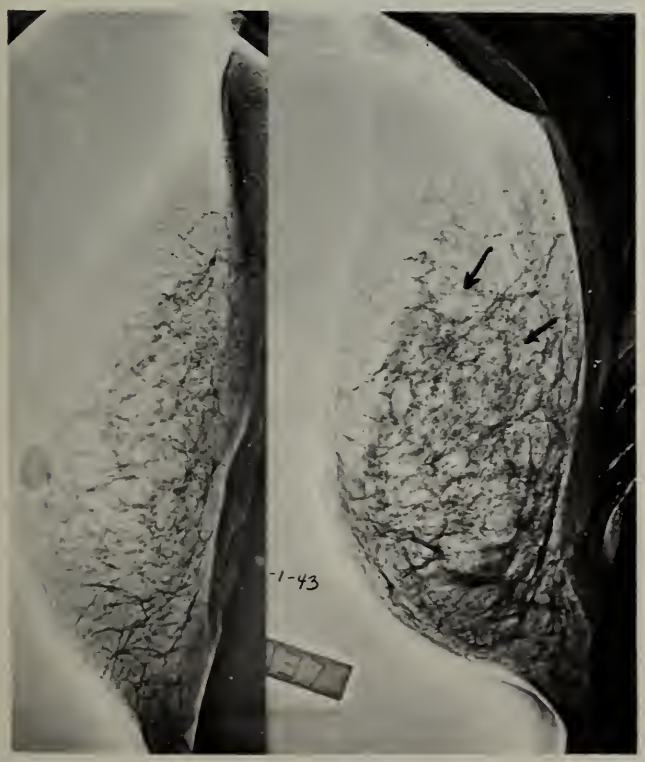


Figure 5.—A 53-year-old patient, previous right mastectomy in 1971. Xeromammography in November 1972 (**left**) shows no definite abnormality. Follow-up study in August 1974 (**right**) shows increased density and ductal activity in upper portion of breast (arrows). Infiltrating lobular and ductal carcinoma was diagnosed at surgical operation.

In ten cases, retrospective review indicated the diagnosis could have been made. In six, breast asymmetry was disregarded. In one, tiny calcifications were overlooked (this latter examination was incomplete. No lateral view was obtained because of temporary technical breakdown and repeat study was not done before biopsy. The breast was clinically suspicious). In one case, architecture and skin changes were disregarded. In another, a tiny nodularity in one portion of the circumference of the wall of a benign appearing cyst eventually proved to be carcinoma arising in the cyst. In one case, increased density and ductal prominence were noted on follow-up xerograms in the remaining breast following previous mastectomy (Figure 5).

Therefore, by rigid and meticulous attention to the criteria for malignancy, the error rate could have been reduced by approximately half, and with greater experience it is hoped that this can be achieved. The higher number of false negative findings, compared with those in Martin and Wolfe's series, have to be attributed to lack of experience. It is recommended that in any group working in this field, one member (with appropriate backup) should be primarily responsible for the xeromammographic program. We must reiterate, however, that in some cases carcinoma simply will not be imaged, and clinical suspicion

TABLE 5.—*Xerographic Findings in Occult Carcinoma*

Calcifications	6
Mass density	8
Mass plus calcifications	4
Asymmetry	2
Architecture change	1

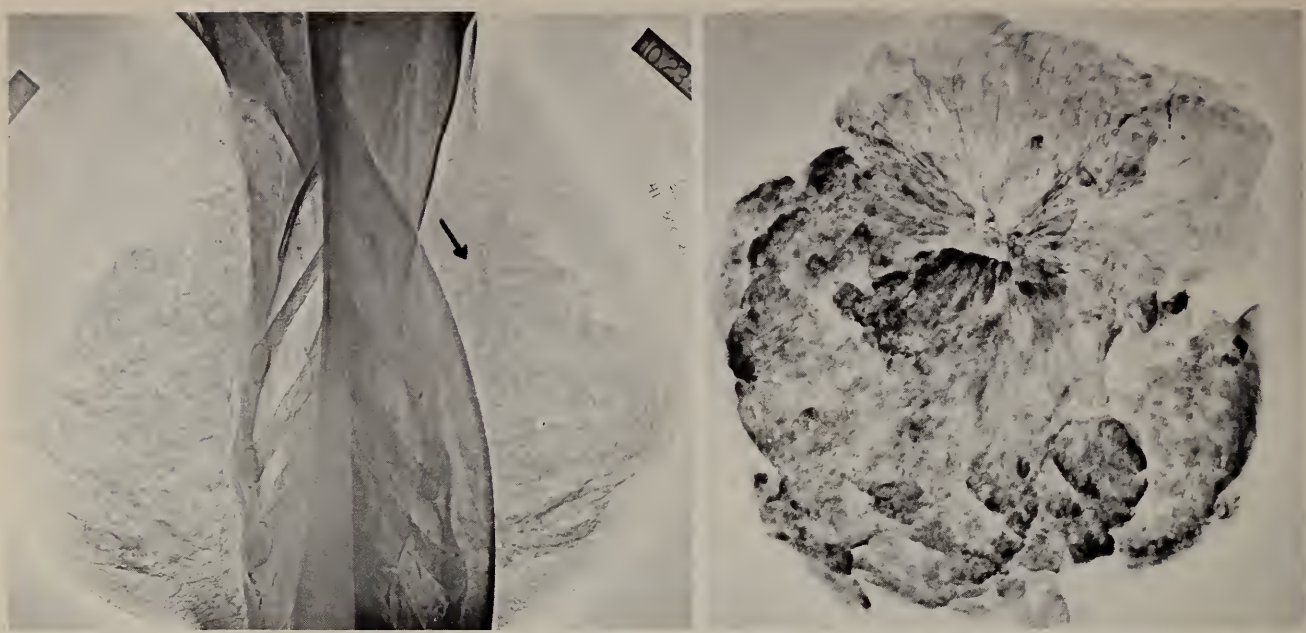


Figure 6.—A 52-year-old patient with two sisters recently operated on for breast carcinoma. No mass palpable. **Left,** xeromammography, done because of family history, shows area of disturbed architecture in upper right breast (arrow) with stellate radiation of strands from a central point, well demonstrated in specimen radiograph. **Right,** pathology was infiltrating lobular carcinoma.

should lead to biopsy despite negative findings on a mammogram. The absolute false negative rate is of course almost impossible to determine because in patients examined there may be undetected carcinoma, reported as negative, which has not come to biopsy.

Clinically Occult Carcinoma

Of course, identifying clinically occult carcinoma is the prime objective in any mammographic program. Our percentage (21 cases out of 2,392 xeromammograms—slightly under 1 percent) is comparable to such percentages in other series (Table 4).[6,9-11] Mammographic findings (Table 5) included calcifications in five cases, mass plus calcifications in four, local mass only in eight, local asymmetry in two (Figure 1), and architecture change in one (Figure 6). In another, in which biopsy was recommended because of stippled calcification in one of many cysts, lobular carcinoma *in situ* was discovered close to but not in the cyst in question. Of the 21 occult cases, 5 had axillary node metastases (24 percent). Of the 76 nonoccult cases, 32 had positive axillary nodes (42 percent). Occult lesions were discovered in patients who were examined for areas of clinical suspicion remote from the eventually discovered carcinoma because of family history, opposite side carcinoma, routine studies in asymptomatic patients, vague pain or discomfort, nipple itching or discharge and clinically non-

Figure 7.—A 69-year-old patient who intermittently felt slight thickening in the right breast. No mass was palpable in this extremely large fatty breast. Classic spiculated carcinoma is seen on xerogram.

suspicious masses. In addition, evaluation for an exceptionally large breast led to xerographic examination (Figure 7). In some cases, though the lesion that eventually proved malignant was pal-

pable, it was not felt to be malignant at the time (and the clinician freely admitted that were it not for findings on a mammogram, biopsy would have been deferred). Another potential situation is that of delay by a patient, despite clinical suspicion of carcinoma, because of fear and denial. The psychological effect of x-ray documentation of clinical suspicion has been decisive in convincing some patients to accept biopsy and treatment.

During the same period at our hospital, 196 biopsies were carried out without xeromammography, 154 with benign and 42 with malignant diagnoses (Table 6). The ratio of benign diagnoses to carcinoma in those patients in whom xeromammography was done (201 to 97) compares favorably in detection rate with those in whom xeromammography was not done (154 to 42). Overall ratio of benign to malignant diagnoses (355 to 139) indicates a high rate of malignant diagnosis in this series, compared with national averages of approximately 4 benign to 1 malignant. This would indicate that we should perhaps be even more aggressive in recommending biopsy.

Discussion

All who use xeromammography owe a debt to the work of Wolfe and Martin,[1-7] whose efforts have made it all possible. The debate over film mammography versus xeromammography will probably never fully be resolved. Suffice it to say that there is more than one way to achieve desired results. In the hands of those proficient and experienced, film mammography can be every bit as effective as xeromammography. It is our opinion, however, that skill in xeromammography is more easily and quickly acquired, with greater ease in information retrieval, by general radiologists. Technical reasons for this have been well described,[1-6] including high resolution, edge enhancement and wide latitude in the images.

Practically speaking, a clinician is interested only in the probability of carcinoma in the overwhelming majority of cases. Descriptions and classifications of benign disease, though of interest, are infrequently of clinical importance. Reliable signs of carcinoma, either definite or leading to increased suspicion, have been well documented[2] and include:

- Localized mass, without complete smooth circular circumscription by surrounding radiolucent fat.
- Clustered or linearly arranged tiny calcifications—spherical, irregular, branching or linear in form.
- Localized ductal prominence, especially if asymmetric.
- Asymmetry in density between similar areas of the two breasts.
- Local disturbance of normal breast architecture, such as stellate radiation of fibrous stranding from a central point, with or without an associated mass.

Secondary signs, such as skin retraction and thickening, nipple retraction, hypervascularity and increased size of axillary nodes, are supportive, but definitely of limited usefulness by themselves. It is well known that some carcinoma simply escapes detection by xeromammography, and that negative findings on a xerogram should never prevent biopsy being done if there is clinical suspicion. It is also true that film mammography may on occasion more readily detect carcinoma that shows only as a poorly defined vague area of increased density.[3] Diagnostic accuracy is definitely decreased in dense dysplastic breasts containing little fat, in any form of mammography. Previous biopsies may cause skin changes, and this information must be available for proper interpretation.

Based on the work of Strax and co-workers,[12,13] the feasibility of mass screening has been established. The relative roles of physical examination, breast self-examination, mammography and thermography are currently being evaluated in the 27 screening centers of the demonstration project of the American Cancer Society and National Cancer Institute.

Early detection criteria designed for use in nonscreening center, private practice situations have been emphasized to our medical staff—with particular emphasis on promoting more thorough breast physical examinations, teaching breast self-examination personally to each patient and classifying patients into high risk categories. Clinical and epidemiological risk factors are numerous,[14] and include previous breast cancer, family history

TABLE 6.—*Total Biopsies Done in the Two-Year Period*

Patients with xeromammography	298
Benign	201
Cancer	97
Patients with no xeromammography	196
Benign	154
Cancer	42
TOTAL BENIGN	355
TOTAL CANCER	139

of breast cancer particularly on the maternal side, late first full-term pregnancy[15] (over approximate age of 30), nulliparous state, Caucasian race, Jewish extraction, higher socioeconomic level, obesity, diabetes, hypertension, other malignancies, early menarche and late menopause. In addition, recent work by Wolfe[16] has categorized women into risk categories based on their mammographic appearance, with those with diffusely dense breasts and those with many areas of ductal prominence having a statistically significant higher incidence of breast cancer.

Based on these criteria, recommendations have been made to our staff that all women at higher risk be clinically examined at least twice a year, in addition to having an annual xeromammogram. Attempts to develop other biologic markers useful for screening are constantly proceeding, but none have yet come into general use.

Finally, it is stressed that in all patients with symptomatic breasts, xeromammography should be done over the approximate age of 35, and from the ages of 25 to 35 if a patient is in a high risk category. In all patients in whom biopsy is done in these groups, xeromammography should be carried out for evaluation of sites other than those clinically apparent, and for baseline study of the opposite breast in the event carcinoma is discovered with resultant mastectomy. Those patients in whom there is nipple discharge should be evaluated by galactography (mammary duct injection)[17] for localization of the usual cause—intraductal papilloma.

REFERENCES

1. Wolfe JN: Xerography of the breast. Radiology 91:231-240, 1968
2. Wolfe JN: Xeroradiography of the Breast. Springfield, Ill., Charles C Thomas, Publisher, 1972
3. Wolfe JN: Xeroradiography—Image content and comparison with film roentgenographs. Am J Roentgenol Radium Ther Nuc Med 117:690-695, 1973
4. Wolfe JN, Dooley RP, Hawkins LE: Xeroradicgraphy of the breast—A comparative study with conventional film mammography. Cancer 28:1569-1574, 1971
5. Wolfe JN: Analysis of 462 breast carcinomas. Am J Roentgenol Radium Ther Nucl Med 121:846-853, 1974
6. Martin JE: Xeromammography—An improved diagnostic method. Am J Roentgenol Radium Ther Nucl Med 117:90-96, 1973
7. Martin JE, Gallagher HS: Mammographic diagnosis of minimal breast cancer. Cancer 28:1519-1526, 1971
8. Threatt B, Appelman H, Dow R, et al: Percutaneous needle localization of clustered mammary microcalcifications prior to biopsy. Am J Roentgenol Radium Ther Nucl Med 121:839,842, 1974
9. Frankl G, Rosenfeld DD: Breast xeroradiography: An analysis of our first seventeen months. Ann Surg 178:676-680, 1973
10. Frankl G, Rosenfeld DD: Xeroradiographic detection of occult carcinoma of the breast. Presented at the 59th Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov 29, 1973
11. Frankl G: Unpublished data. Presented at the 14th Annual Conference on Detection and Treatment of Early Breast Cancer. San Juan, Puerto Rico, March 10, 1975
12. Strax P, Venet L, Shapiro S, et al: Mammography and clinical examination in mass screening for cancer of the breast. Cancer 20:2184-2188, 1967
13. Strax P, Venet L, Shapiro S: Value of mammography in reduction of mortality from breast cancer in mass screening. Am J Roentgenol Radium Ther Nucl Med 117:686-689, 1973
14. Papaionnou AN: Etiologic factors in cancer of the breast in humans. Surg Gynecol Obstet 138:257-287, 1974
15. MacMahon B, Cole P, Lowe CR, et al: Age at first birth and breast cancer risk. Bull WHO 43:209, 1973
16. Wolfe J: Identification of the patient who is at high risk for developing breast cancer. Presented at the 14th Annual Conference on Detection and Treatment of Early Breast Cancer. San Juan, Puerto Rico, March 10, 1975
17. Threatt B, Appelman HD: Mammary duct injection. Radiology 108:71-76, 1973

VD PLACARD

In view of the increasing incidence of venereal disease and the unknown incidence of asymptomatic gonorrhea, especially in women, the California Medical Association recommends that a gonorrhea culture test be carried out more frequently for women between 15 and 45 years of age.

This sign could be displayed in your waiting room or preferably in your examining room and would serve to encourage patients to request a test. Remember that we consider a sign only one aid to communication between you and your patient to introduce the subject of venereal disease. It is of course not a replacement for your responsibility or judgment about your patient's care.

This placard is perforated so that it can be removed from the Journal and displayed in a standard 8″ × 10″ frame. Choose the side of the sign that appeals to you more. Additional copies of the sign are available without charge. Write to the Venereal Disease Task Force, California Medical Association, 731 Market Street, San Francisco 94103.

Refer to: Holmes KK: Screening and the detection of gonorrhea. West J Med 123:367-371, Nov 1975

Screening and the Detection of Gonorrhea

KING K. HOLMES, MD, PhD, *Seattle*

The purpose of a physician's screening for gonorrhea is the provision of comprehensive health care to patients who seek his care. Among sexually active young patients, gonorrhea is probably far more common than many other diseases a physician "screens" for during a routine physical examination. Since gonorrhea culture tests are too costly in time and money to be offered to every patient, guidelines can be used to select patients for screening who are most likely to have gonorrhea. The gonorrhea culture test should be carried out in the same spirit as a cervical cytology test, as a potential health benefit and without stigma.

However, even more important than gonorrhea screening, from the standpoint of the patient, is (1) increased use of culture for diagnostic problem solving, particularly in women with dysuria, abnormal vaginal discharge, abnormal menstrual bleeding or lower abdominal pain, and (2) location and treatment of sex partners.

INCREASED FEDERAL SPENDING for venereal disease control in the United States since 1972 has been directed at gonorrhea case detection, by identification and treatment of infected sex partners of men with gonorrhea, and by detection of nonsymptomatic gonorrhea in women using routine screening endocervical culture examinations. Since 1972 the number of cultures carried out as part of the screening program rose each month, reaching about 700,000 per month in the spring of 1974, and remaining constant thereafter. The percentage of cultures which yielded Neisseria gonorrhoeae fell from about 8 percent in 1972 to about 4 percent in mid-1973, and has remained just over 4 percent since then.

As summarized in Table 1, the number of positive cultures obtained as a result of this federally-funded program during the 12-month period ending June 30, 1974 was 345,090—rep-

From the Departments of Medicine, U.S. Public Health Service Hospital, and the University of Washington School of Medicine, Seattle.

Submitted June 9, 1975

Reprint requests to: King K. Holmes, MD, PhD, U.S. Public Health Service Hospital, 1131 Fourteenth Avenue South, Seattle, WA 98114.

resenting 4.3 percent of all cultures carried out during this period.[1] The inclusion of 148,976 positive cultures from women examined in venereal disease clinics within the total number of positive "screening" cultures listed in Table 1 suggests a need to reach a common understanding of the term "screening" as applied to gonorrhea case detection.

Proposed Definition of Terms Applied to Gonorrhea Case Detection

Approximately 38 percent of women named as gonorrhea contacts in Table 1 had positive cultures, and N. gonorrhoeae typically may be recovered from three quarters of women named as suspected source contacts of men with acute gonococcal urethritis. Similarly, we have found that about 50 percent of women with suspected pelvic inflammatory disease have gonococcal infection. To imply that cultures carried out on women named as suspected source contacts or on women with symptomatic disease are "screening" cultures is to take a somewhat hopeless view of the utility of the medical history and physical examination in diagnosis. It also serves to inflate the relative value of true screening, as opposed to the values of contact tracing and of clinical acumen in gonorrhea case detection. The following classification of case detection methods may appear self-evident, but the terms are nontheless confused in common usage.

- *Screening Examination for Gonorrhea:* This refers to routine testing of persons who are truly nonsymptomatic or who have symptoms totally unrelated to gonorrhea. When applied to *patients* who have sought a physician's care for an unrelated problem, the term case finding may be more appropriate than screening, but the latter term will be used in this discussion. Screening is thus distinguished from the following two categories.
- *Contact Tracing:* This is the total process by which sex partners of infected patients are identified, notified and examined by appropriate diagnostic laboratory tests for gonorrhea.
- *Diagnostic Problem Solving:* This is the appropriate use by clinicians of diagnostic tests for gonorrhea to solve clinical diagnostic problems in patients who present with symptoms or signs suggestive of, or compatible with, gonorrhea. These manifestations in women include lower abdominal pain, abnormal vaginal discharge, dysuria and urinary frequency, rectal symptoms, joint pains and skin lesions, and probably include abnormal menstrual bleeding.

Misconceptions About Symptomatic Versus Nonsymptomatic Gonorrhea

Most beliefs concerning the clinical epidemiology of gonorrhea derive from the experience of physicians working in venereal disease clinics, rather than from probability sampling, case control or cohort studies, or from the syndrome-oriented experience of physicians in general practice or of certain subspecialties—such as rheumatology and gynecology. Recent evidence suggests that the sample bias represented by patients seen in venereal disease clinics has produced a distorted set of heuristic principles which are leading to systematic errors in the approach of educators and public health workers to the control of gonorrhea. Analysis of these principles is important in evaluating the potential of screen-

TABLE 1.—*Results of Gonorrhea Culture Tests on Females in the United States, July, 1973 through June, 1974**

Source of Test	*Number Tested*	*Number Positive*	*Percent Positive*
Health Department—VD clinic	783,838	148,976	19.0
Health Department—Non-VD clinic	1,474,248	48,105	3.3
Public-Private hospital—outpatient	1,347,847	52,675	3.9
Public-Private hospital—inpatient	60,059	1,658	2.8
Community health centers	591,452	17,492	3.0
Private physicians	2,286,743	44,540	1.9
Private family planning groups	795,738	16,061	2.0
Group health clinics	105,587	3,083	2.9
Industrial screening	17,687	318	1.8
Student health center	230,624	3,550	1.5
Military/dependents	150,251	2,103	1.4
Manpower training agency	11,441	690	6.0
Correction or detention centers	46,512	2,378	5.1
Other	114,852	3,461	3.0

*Source: Morbidity and Mortality 23:363-364, 1974.

ing, relative to the other two methods listed above for gonorrhea case detection.[2]

• *Symptoms of Gonorrhea in Women:* It is held that gonorrhea in women is usually nonsymptomatic, because infected women seen in venereal disease clinics are most often brought to treatment as contacts rather than as self-referred patients with symptoms. However, 80 percent of women seen with gonorrhea in the University of Washington specialty clinics and emergency room have sought treatment because of acute symptoms. This illustrates the importance of perspective and sample bias in determining one's perception of the frequency of symptoms in women with gonorrhea. Even among women seen as source contacts in a venereal disease clinic, abnormal vaginal discharge is common. It is argued that gonorrhea is not more common in female venereal disease clinic patients with vaginal discharge than in those without vaginal discharge. However, the issue is whether women at large in the community with vaginal discharge have a higher prevalence of gonorrhea than women without vaginal discharge (this would require study by population-probability sampling), or whether women who acquire gonorrhea acutely develop symptoms, at least transiently (this would require a prospective cohort study). We should therefore acknowledge that it is unknown whether 10 percent or 90 percent of women who acquire gonorrhea develop associated symptoms. Is it then more important to advocate intensified screening to find gonorrhea in nonsymptomatic women and to teach women that they should seek regular checkups because gonorrhea usually produces no symptoms in women; or is it more important that women (and physicians) be educated to suspect gonorrhea whenever certain symptoms develop?

• *Symptoms of Gonorrhea in Men:* It is currently in vogue to state that 10 to 20 percent of men with gonorrhea are nonsymptomatic, because currently 10 to 20 percent of male venereal disease clinic patients with gonorrhea have no symptoms. Again, this bears no relationship to the true proportion of new cases of gonorrhea in men who never become symptomatic (in an unpublished cohort study we have found this proportion is only 3 percent) or to the proportion of all cases of gonorrhea in men in the universe at any point in time who are nonsymptomatic (this proportion has been found to be greater than 50 percent in several studies). More important, the prevalence of nonsymptomatic gonorrhea in infected men named as source contacts by self-referred women with symptomatic acute gonorrhea or with gonorrhea detected by routine screening is also about 50 percent, which only reflects the percentage of men with gonorrhea in the community who are nonsymptomatic. Would it therefore be more productive to search for cases of nonsymptomatic gonorrhea in men by screening large numbers, or to trace suspected male source contacts named by self-referred women with gonorrhea?

Potential of Screening for Nonsymptomatic Gonorrhea

Having discussed the definition of "screening" for gonorrhea and the uncertainty concerning the relative predominance of nonsymptomatic versus symptomatic gonorrhea in women, we can turn to a discussion of the potential of screening methods for gonorrhea. The potential of screening can be evaluated from the standpoints of the sensitivity and specificity of available or potentially available screening methods, from the standpoint of cost-effectiveness and from the standpoint of the maximum potential impact of screening upon the incidence of gonorrhea and the complications of gonorrhea—if unlimited funds were available for screening.

The method currently best suited for screening for nonsymptomatic gonorrhea in women is of course the endocervical culture. Table 1 shows that 196,114 (2.7 percent) of 7,233,041 women screened by health care providers (excluding venereal disease clinics) had positive cultures. The percentage positive ranged from 1.4 percent among military dependents to 6.0 percent of participants in a manpower training program for indigent women. It should be emphasized that most of these figures are derived from clinics attended by some women who seek care because of symptoms of gonorrhea; this is even true in the family planning clinics. The prevalence figures listed in Table 1 are therefore probably higher than the actual prevalence of gonorrhea in the communities served by the various clinics.

The cost-effectiveness of screening for gonorrhea is inversely proportionate to the cost of the screening method used and is directly proportionate to the prevalence of infection in the population screened. In Seattle,[3] the prevalence of gonorrhea among women (symptomatic plus nonsymptomatic) examined by private physicians has been shown to be independently positively corre-

lated with age (maximum prevalence in adults 30 or under), low socioeconomic status, race (maximum prevalence in nonwhites) and marital status (maximum prevalence in single or divorced women). Cost-effectiveness could therefore be optimized by screening only women 30 or under who have at least one of the other three risk factors listed above. For example, the prevalence of gonorrhea was 8 percent in Seattle women under 30 and of low socioeconomic status who consult a private physician. One additional risk factor which should lead to a screening test for gonorrhea in women of any age is the presence of another venereal disease. Another technique which might be termed "screening" involves the routine reexamination of women four to six weeks after curative treatment for gonorrhea, in order to detect reinfection. This has disclosed recurrent gonorrhea in about 15 percent of a series of women reexamined during a Communicable Disease Center (CDC) sponsored study in Montgomery, Alabama. Finally, a screening culture for gonorrhea is often done during pregnancy, even in low prevalence groups, because of the possible additional risk of gonorrhea upon the pregnancy itself[4] and for the fetus.

In summary, the cost-effectiveness of screening for gonorrhea can be optimized by selection of patients to be screened on the basis of the following risk factors: age, socioeconomic status, marital status, race, presence of another venereal disease, recent treatment for gonorrhea, and pregnancy. Alternatively, a frank discussion of a patient's sexual behavior is probably the most specific method for selection of high risk patients.

Two attractive supplements to endocervical culture screening for gonorrhea are culturing the sediment of urine specimens submitted to clinical laboratories and serologic testing. A strong case should be made for routine attempts to recover N. gonorrhoeae from the sediment of urine specimens submitted to microbiology laboratories from young female patients with symptoms of urinary tract infection. The additional cost over that of routine cultures for coliforms is small, and the potential yield is high. Concerned physicians should consult with their laboratory consultants to implement this as a matter of policy. Chapel and Smeltzer found that cultures of urine sediment were 82 percent as productive as cultures of the endocervix in detecting gonorrhea in women.[5]

Serologic Tests for Screening for Gonorrhea: Although the serologic diagnosis of gonorrhea is under active study, no serologic test has yet been convincingly shown to have better than a 60 percent sensitivity in detecting gonorrhea in nonsymptomatic women, unless paired sera are available for study. Another problem with serologic tests is the occurrence of false positive reactions. Bayes theorem for posterior probability, as applied to gonorrhea case detection, predicts that the probability (P) that gonorrhea is present in a patient, given that a serologic test for gonorrhea is reactive, is proportional to the prevalence of gonorrhea in the population:

$$P = \frac{\text{Prevalence} \times \text{Sensitivity}}{(\text{Prevalence} \times \text{Sensitivity}) + (1 - \text{Prevalence}) \times (1 - \text{Specificity})}$$

where specificity is defined as the proportion of uninfected patients having negative findings on a serologic test. This predicts that when a serologic test is used to screen for gonorrhea, a progressively smaller proportion of those who react are actually infected as the prevalence of gonorrhea in the population falls.

This appears to be borne out in our own experience. For example, in using a latex agglutination test for gonorrhea in a gynecology population having a 13 percent prevalence of gonorrhea, the probability of gonorrhea among women having a reactive latex agglutination test was 23 percent. In a prenatal population having a 2 percent prevalence of gonorrhea, the probability of infection, given a reactive test, was only 13 percent. The probability of gonorrhea, given a reactive serologic test, also is inversely proportional to the ratio:

$$\frac{\text{Average Duration of Persistent Antibody}}{\text{Average Duration of Persistence of Infection}}$$

Neither of these durations is known at present.

Should Clinical Laboratories Confirm Gonococcal Isolates by Sugar Fermentation Reaction? An important prediction of Bayes theorem is that the significance of "positive" culture test results might also fall as the prevalence of gonorrhea falls. Stating this another way, if a given laboratory recovers Moraxella osloensis from 0.5 percent of cultures, and usually confuses this organism with N. gonorrhoeae, this would not be a major source of confusion in a venereal disease clinic, where 35 per- of women cultured have gonorrhea; but this would cause very frequent false positive interpretations of cultures obtained by screening a prenatal population where the prevalence of gonorrhea was only 1 percent. We believe this is a real problem, and that it is absolutely essential for a clinical laboratory receiving routine genital screening cultures from a low prevalence popu-

lation to carry out sugar fermentation tests to confirm the identity of each putative gonococcal isolate.

One final point should be considered in assessing the potential impact of screening for gonorrhea. The cost-effectiveness of culture screening for gonorrhea is highest among women who have the highest prevalence of gonorrhea. It has long been assumed that certain groups have a high prevalence of gonorrhea because they are the most promiscuous. Another tenable hypothesis is that the high prevalence of gonorrhea in certain groups is instead attributable to poor health care services or poor illness behavior of such groups; that is, that after becoming infected, certain groups of patients do not seek or obtain proper treatment for themselves and their sex partners. Since the application of screening methods currently involves getting the patient into the physician's office, how will screening be applied to the very high prevalence populations where screening would be most effective, even if unlimited funds were available for screening? Perhaps the major challenge in using screening for gonorrhea lies in selling the idea of preventive care and making it available to those who most need it.

REFERENCES

1. Morbidity and Mortality 23:363-364, 1974

2. Tversky A, Kahneman O: Judgement under uncertainty: Heuristics and biases. Science 185:1124-1131, 1974

3. Pedersen AHB, Bonin P: Screening females for asymptomatic gonorrhea infection. Northwest Med 70:255-261, 1971

4. Handsfield HH, Hodson WA, Holmes KK: Neonatal gonococcal infection—I. Orogastric contamination with *Neisseria gonorrhoeae*. JAMA 225:697-701, 1973

5. Chapel TA, Smeltzer M: Culture of urinary sediment for the diagnosis of gonorrhea in women. Br J Vener Dis 51:25-27, 1975

First Signs of Anaphylaxis

Usually you see a general flush, urticaria, paroxysmal coughing and, as symptoms get worse and worse, the patient has a severe feeling of anxiety with a little dyspnea and then orthopnea, cyanosis and shock. If it is within the first 15 minutes, it is going to be a very major anaphylaxis.

—JOHN ARTHUR MAY, MD, *Portland, OR*
Extracted from *Audio-Digest Family Practice,* Vol. 23, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angees, CA 90057.

Medical
PROGRESS

Refer to: Bennett WM: Principles of drug therapy in patients with renal disease (Medical Progress). West J Med 123:372-379, Nov 1975

Principles of Drug Therapy in Patients with Renal Disease

WILLIAM M. BENNETT, MD, *Portland*

Patients with reduced renal function commonly require drug therapy for various associated conditions. Most drugs are fully or partially excreted by the kidney; therefore, drug dosage regimens often need to be adjusted in order to provide safe yet effective treatment for patients with renal disease. In addition, certain therapeutic agents have potential nephrotoxicity and pharmacologic actions that may jeopardize already compromised renal function. Understanding of drug pharmacology, the therapeutic dose and the speed of drug elimination in a given patient will lead to correct assessment of the drug regimen.

WIDESPREAD AVAILABILITY of facilities to care for patients with chronic renal disease has notably increased the numbers and types of patients presenting themselves to physicians for long-term medical management. Coexisting diseases and age no longer present insurmountable obstacles to application of dialysis and transplantation. Coincident with this trend has been a proliferation of newer and more potent therapeutic agents available for treatment. Most drugs are fully or partially excreted by the kidney; therefore, drug dosage regimens often need to be adjusted in order to provide safe yet effective treatment for patients with renal insufficiency. In addition, the altered biochemical milieu imposed by chronic renal disease may lead to adverse effects with many common drugs. Indeed, certain therapeutic agents have potential nephrotoxicity and pharmacologic actions that can jeopardize already compromised renal function. The present communication will present a theoretical basis for renal failure dosage adjustments and some practical guidelines for constructing these therapeutic regimens. The subsequent discussion has as its basis the general principle that correct assessment of a drug regimen requires knowledge of the pharmacology of the drug, the therapeutic dose and the speed of elimination in a given patient.

The basic factors and determinants of any drug's pharmacologic effect are absorption, distribution in body fluids and drug elimination. A schematic representation of these drug pharmacokinetic processes is shown in Figure 1. These factors as they relate to a patient with renal disease will be handled separately in the following sections.

Drug Absorption from the Gastrointestinal Tract and from Intramuscular Injection Sites

When a drug is in solution, some important determinants of its absorption are the character of the membranes it must cross to reach the circulation, blood flow at the absorption site, surface

From the Division of Nephrology, Department of Medicine, University of Oregon Health Sciences Center, Portland.

Reprint requests to: W. M. Bennett, MD, Department of Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

ABBREVIATIONS USED IN TEXT

C = concentration of the drug in the blood
Cl_{Cr} = creatine clearance
C_0 = concentration in the blood at zero time assuming instant mixing
D_L = loading dose
GFR = glomerular filtration rate
K% = the overall rate constant for elimination of the drug from the body as a percent per hour
pKa = the pH at which the drug is in equilibrium between the ionized and un-ionized state
t½ = half-life
V_D = volume of distribution
X_B = amount of drug in the body

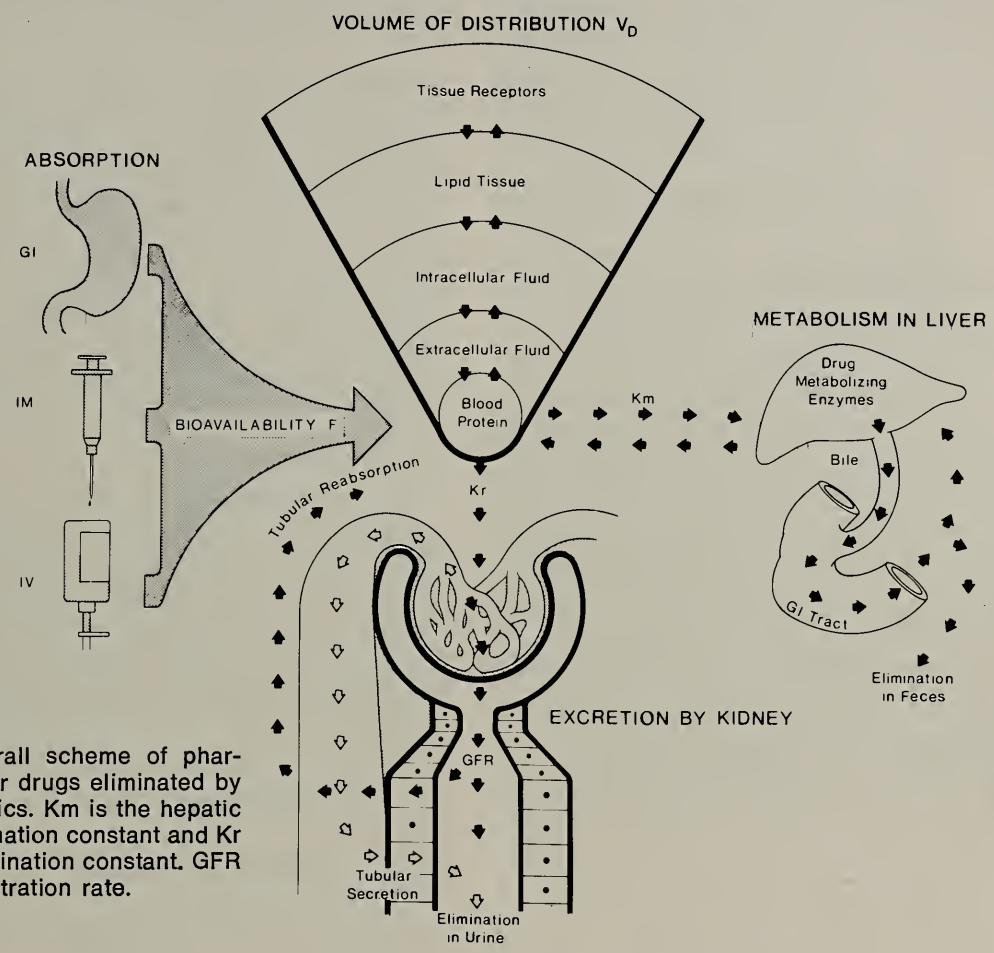


Figure 1.—Overall scheme of pharmacokinetics for drugs eliminated by first order kinetics. Km is the hepatic metabolic elimination constant and Kr is the renal elimination constant. GFR is glomerular filtration rate.

area available for absorption and contact time between drug and absorption surface. The physiochemical properties of the drug, such as lipid solubility, pKa and molecular size, are obviously also critical. Little is known specifically about variability in drug absorption in human renal failure, but certainly the gastrointestinal disturbances in renal failure (nausea, vomiting, diarrhea and gastrointestinal tract edema) could alter absorption. In addition, many drugs may add to gastrointestinal symptoms experienced by uremic patients by either local irritative or other pharmacologic actions. Edematous patients in general absorb drugs more slowly from intramuscular injection sites.

Drug Distribution

Each drug distributes through the body in a characteristic manner. The apparent volume of distribution (V_D) is given by dividing the amount of drug in the body (X_B) by the concentration of the drug in the blood (C), or $V_D = \frac{X_B}{C}$. This volume of distribution can be simply estimated by plotting drug concentration versus time on semilogarithmic paper as is shown in Figure 2. Extrapolation of the straight portion of the log-linear curve back to zero time yields the value for C_0, the concentration in the blood at zero time assuming instant mixing. Since instant mixing does not usually occur, this value is only at best an esti-

mate. By dividing C_0 into the administered dose adjusted for the percent absorbed, the apparent volume of distribution is obtained.

Once V_D has been derived for a drug, it may be used to calculate the amount of drug remaining in the body when the plasma concentration is known and falls on the exponential portion of the decay curve; or, conversely, it may be used to predict the initial blood level—that is, C_0—following a given dose. (For example, for gentamicin, $V_D = 15$ liters. An 80 mg dose should then give a blood level of 5.3 micrograms (μg) per ml.) It should be emphasized that the V_D is not necessarily equal to an identifiable anatomical compartment, but is a mathematical concept used to relate the dose of a drug to the plasma concentration achieved by that dose. Although the volume of distribution for any drug seems to be a characteristic of the drug, this measurement may be altered by disease. Edema and ascites tend to increase V_D, whereas dehydration and upright posture tend to decrease it.[1] This is usually only of clinical importance when the V_D is relatively small (such as <50 liters). Lipid soluble molecules preferentially penetrate the central nervous system and have a large V_D, whereas high affinity for plasma proteins may restrict drugs to the intravascular space and decrease V_D. Drugs bound tightly to tissue receptors, such as digitalis glycosides, tend to have very large volumes of distribution. Renal disease may either increase or decrease V_D so that no general statement can be made.

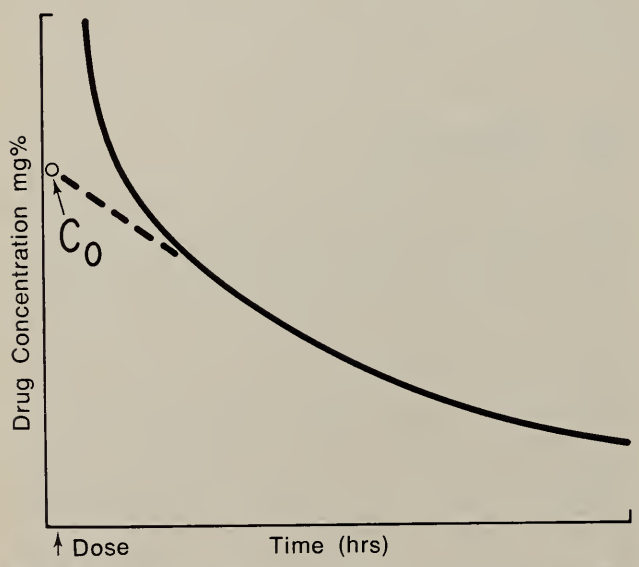


Figure 2.—Theoretical log-linear plot of drug concentration in blood against time for a drug eliminated by first order kinetics. C0 is the concentration achieved at zero time assuming complete and instant mixing.

Drug Elimination

Most drugs are eliminated from the body by first order kinetics, that is, the amount of drug eliminated from the body in a unit of time is proportional to the amount of drug in the body at that time. The rate of drug removal is usually expressed by its half-life ($t\frac{1}{2}$). Factors which modify this rate include the volume of distribution, renal function, extent of tissue binding, lipid solubility and hepatic drug metabolism.

Mathematically, $t\frac{1}{2} = \frac{.693}{K}$ where K is an elimination rate constant which reflects the above variables of total body drug clearance. The elimination constant can be expressed by the formula $K = \frac{k_r + k_m}{V_D}$ where k_r is the renal elimination constant and k_m is the hepatic metabolic elimination constant.[2] This assumes little drug is lost by sweat or gastrointestinal secretion. If one then substitutes for K in the half-time formula, it becomes $t\frac{1}{2} = \frac{.693 \times V_D}{k_r + k_m}$.

It becomes obvious that $t\frac{1}{2}$ will be prolonged when either V_D is increased and/or the rate of renal clearance or hepatic metabolism decreases. The maximum achievable total body drug clearance would then approximate the sum of renal and hepatic blood flow, that is, 3 liters per minute. An example of the effect of incremental decrease in renal clearance on the $t\frac{1}{2}$ is shown in Table 1, for a theoretical drug.

Renal Handling of Drugs

The rate of drug elimination through the glomerulus depends on the glomerular filtration rate, the concentration of drug in the blood and the proportion that is bound to plasma proteins. Tubular reabsorption of the drug may occur, and tends to be rather complete with lipid soluble compounds. Many pharmacologic agents are

TABLE 1.—*The Effect of the Decrease in Renal Clearance on Drug Half-life*

V_D (liters)	Renal drug clearance (ml/min)	$t\frac{1}{2}$ (min)
15	700	15
15	100	104
15	50	208
15	10	1,020
15	2	5,220

V_D = volume of distribution
$t\frac{1}{2}$ = half-life

weak acids or weak bases, and are transported from the peritubular blood into the urine by various tubular secretory mechanisms. Secretion of these compounds tends to be influenced by other drugs competing for transport sites. An example is the diminution of methotrexate excretion by salicylate and other organic anions. Some common drugs that use the weak acid secretory system for elimination are the thiazide diuretics, sulfonamides, penicillins, probenecid and methotrexate.

Other drugs that are weak acids or bases may have their excretion modified by luminal pH. This depends on the pKa of the compound, which is the pH at which the drug is in equilibrium between the ionized and un-ionized state. At low urine pH, weak acids with low pKa tend to be more un-ionized and thus more easily reabsorbed, whereas if urine pH is increased, ionization and urinary excretion are enhanced. Table 2 includes some agents whose excretion is modified by urinary pH.

In general, manipulation of urinary pH by alkalinization or acidification is successful in enhancing excretion of drugs when the drug is normally excreted by the kidney rather than metabolized by the liver, or if metabolic pathways are saturated by large quantities of drug. Other helpful factors include a pKa in the range of achievable urinary pH (5.0 to 8.0), and greater water than lipid solubility.

Drug Metabolism or Biotransformation

Many drugs are metabolized to inactive compounds before excretion. These processes usually take place in the endoplasmic reticulum of hepatic cells under the influence of drug metabolizing enzymes. These enzymes may oxidize, reduce, hydrolyze or conjugate drugs to more polar compounds which are then pharmacologically inactive, water soluble and more easily excreted in the urine. In general, oxidation of drugs is normal in renal failure[3] or may even be accelerated. The latter has been described for diphenylhydantoin, although decreased protein binding and higher "free" levels may contribute to increased removal.[4] Few drugs undergo reduction reactions; however, the reduction of hydrocortisone has been shown to be decreased in renal failure.[5] Glucuronidation is normal in uremia, while many acetylation reactions are slowed. It becomes obvious that knowledge of any given drug's metabolic fate is necessary to predict metabolic alterations produced by renal failure. Some metabolic transformations of common drugs and the effects of uremia are listed in Table 3.

TABLE 2.—*Drugs with Excretion Enhanced by Altering Luminal pH*

Enhanced excretion in alkaline urine (pH>7)	*Enhanced excretion in acid urine (pH<5)*
Acetazolamide	Amitryptyline
Phenobarbital	Amphetamine
Phenylbutazone	Imipramine
Sulfonamides	Meperidine
Salicyclic acid	Quinine
	Quinidine
	Chloroquin

Increased Sensitivity to Drugs

Reduced plasma protein binding of drugs in renal failure (such as barbiturates, narcotics and diphenylhydantoin) will increase the unbound or free fraction of the blood concentration of drug. Enhanced and prolonged pharmacologic effects may result.[6] In addition, the blood-brain barrier may be altered in uremia, promoting increased drug uptake within the central nervous system. Care must be taken in prescribing drugs with decreased plasma protein binding to uremic patients, especially those with low serum proteins.

Altering Dosage in Renal Failure

When patients receive multiple dose regimens at uniform dose intervals, the average plasma concentration accumulates until a steady state concentration is reached. Under such circumstances, the time required to reach approximately 90 percent of the steady state drug concentration is 3.3 times the t½. Since the t½ may be greatly prolonged in renal failure, effective therapy may be greatly delayed if maintenance dosage is given adjusted to the renal failure t½. Therefore, a loading dose is usually necessary to achieve acceptable initial therapeutic effectiveness. This principle is particularly applicable when planning antibiotic and digitalis therapy. For practical purposes, the usual initial drug dosage is not changed unless the drug in question has a narrow toxic-therapeutic ratio or there is an altered V_D (as in edema or obesity). Most studies which consider alteration of drug regimens in renal failure have involved antibiotics. Adjustment of dosage is usually dictated by the prolongation of t½ which is, in turn, estimated by the degree of reduction in glomerular filtration rate. Since the usual clinical determinations of serum creatinine or creatinine clearance do not

TABLE 3.—*Effects of Uremia on Metabolism of Common Drugs (Adapted from Reidenberg[3])*

Metabolic Process	*Drug*	*Effect of Uremia*
Oxidation	Acetohexamide	? slowed
	Dephenylhydantoin	Drug metabolite induces increased oxidation
	Phenacetin	None
	Phenobarbital	None
	Quinidine	None
	Tolbutamide	None
Reduction	Hydrocortisone	Slowed
Ester hydrolysis	Procaine	Slowed
Tissue peptide degradation	Insulin	Slowed, probably due to lack of renal metabolism
Glucuronidation	Chloramphenicol	None
	Indomethacin	None
	Tyroxine	None
	Triiodothyronine	None
Acetylation	Hydralazine	Slowed in some people*—genetically determined slow acetylators
	Isoniazid	Slowed in genetically determined slow acetylators*; normal in fast acetylators
	Paraamino salicylic acid	Slowed
	Sulfonamides	Slowed

*True also of a normal population.

reflect true glomerular filtration rate or overall renal function (such as tubular mechanisms), these recommended adjustments are only first approximations at best. Increasing use of available serum drug concentrations should improve therapy.[7]

These levels can be interpreted fully only if the elapsed time from the last dose and the t½ in that particular patient are known. To obtain the best estimate of the peak blood concentration, blood should be sampled one to two hours after an oral dose and one hour after an intravenous or intramuscular dose. Caution must be exercised when interpreting results from drugs which have altered drug-protein binding in uremia since free and pharmacologically active levels may be increased despite normal total drug levels. Likewise, when metabolic processes produce pharmacologically active metabolites (such as azathioprine and propranolol) normal or low serum levels of the original drug may be misleading.

Various strategies can be used when devising dosage schedules in renal failure. The most commonly used methods are the constant dose-varying interval method and the reduced dose-constant interval method. The former is simple to apply but produces peaks and valleys in serum levels of drug while the latter produces more constant blood levels but necessitates fractions of usual dosages. Some drugs lend themselves to constant intravenous infusions, and although therapy can be precisely adjusted, the complexity and monitoring required make routine use impractical. A new method, proposed by Orr and co-workers,[8] employing the occupancy principle which involves calculating the time during which a drug resides in a certain body space, has not yet attained wide acceptance. The use of these strategies is illustrated in the following sections describing techniques for administering various commonly used pharmacologic agents to patients with renal failure.

Antimicrobial Therapy

The basic goal of antibiotic therapy is to achieve a steady state blood and tissue level which is both effective and nontoxic. Ideally, the steady state concentration will oscillate with time so that the lowest concentration would exceed the minimum value necessary to kill the organism in question, and the peak concentration is below the level which gives side effects or toxicity. Since with antibiotic therapy the patient is most ill when the drug is first given, a loading dose should be administered. Therefore, a usual or even slightly increased initial dose should be given to ill patients with renal failure.

To adjust maintenance therapy for renal failure, one of several approaches can be used. Dettli and co-workers[2] and Wagner[9] have suggested the following approach which requires knowledge concerning the relationship between the overall rate constant for elimination of the drug from the body as a percent per hour (K%)

and the creatinine clearance (Cl_{Cr}). This is shown in Figure 3. Mathematically, $K\% = a + b\ Cl_{Cr}$, where K% is the overall elimination rate constant, a is the portion of elimination rate constant due to nonrenal losses, and b Cl_{Cr} is the portion of the elimination rate constant due to renal losses of the drug. Graphically, a is the intercept on the y axis of K% plotted versus Cl_{Cr}, and b is the slope.

To calculate the elimination t½ for any given value of K% in renal failure, use the formula $t\frac{1}{2} = \frac{69.3}{K\%}$. To make dosage adjustment for renal impairment, use the equation $D_r = D_m \times \frac{\text{patient } K\%}{\text{normal } K\%}$, where D_r is the dose in renal failure and D_m is the usual maintenance dose.

In order to plan gentamicin therapy for a 70-kg patient with renal failure and a Cl_{Cr} of 10 ml per minute, a normal volume of distribution the same as extracellular fluid (15 liters) and a desired peak blood level of 10 μg per ml are assumed. Since the loading dose (D_L) is not altered in renal failure, it can be calculated by rearranging the formula $V_D = \frac{D_L}{C}$, to $D_L = V_D \times C$. $D_L = 15$ liters $\times 10$ μg per ml, which gives a result of $D_L = 150$ mg or 2.1 mg per kg. Maintenance doses can be calculated as illustrated below. Values for the constants a and b are obtained from a data table, and normal creatinine clearance is assumed to be 100 ml per minute. Using the overall formula $K\% = a + b\ Cl_{Cr}$, the normal K% for gentamicin is equal to $2 + .28 \times 100$ ml per minute. It then follows that $K\% = 2 + 28$, or $K\% = 30$. The K% in the theoretical patient is equal to $2 + .28 \times 10$ ml per minute, or 4.8. Thus, the maintenance dose for our patient is equal to 70 (the usual maintenance of 1 mg per kg for a 70-kg person) times 4.8 (the K% for the theoretical patient), divided by 30 (the normal K%). Calculating through, the new maintenance dose is equal to $70 \times \frac{4.8}{30}$, or 11 mg. This 11 mg can be given at the usual dosage time interval of eight hours. Data for the appropriate constants as derived from the literature[7,8] are compiled in Table 4. The t½ in the theoretical patient would be $\frac{69.3}{4.8}$, or approximately 14.5 hours.

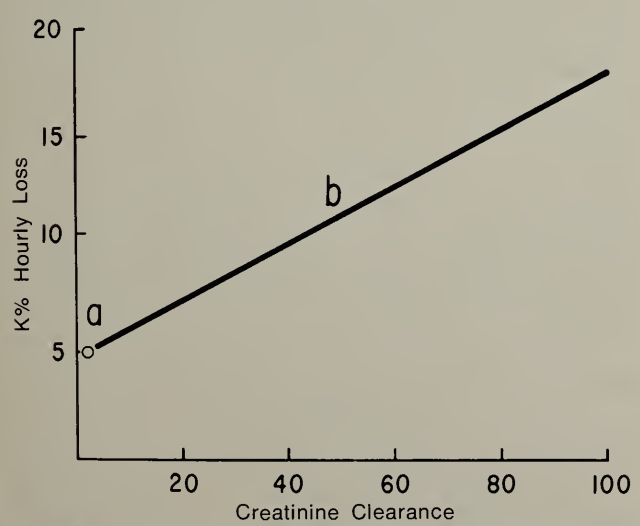


Figure 3.—Relationship of the overall elimination constant K% expressed as hourly percent loss and creatinine clearance. The a is percent hourly loss due to nonrenal processes and b is slope of the line.

Simpler methods have evolved for the commonly used aminoglycoside antibiotics using the t½. These drugs are usually excreted unchanged in the urine and have little metabolic transformation. The t½ can be related to the glomerular filtration rate (GFR) and serum creatinine in such a way that a 50 percent loss of renal function results in a doubling of the t½.[10]

For kanamycin, the t½ in hours equals three times serum creatinine. Normal dosage interval is 12 hours (every third t½, since normal t½ is four hours). Therapeutic serum level is 10 to 30 μg per ml, and a loading dose of 7 mg per kg of

TABLE 4.—*Elimination Constants and Slopes for Various Antibiotics (Adapted from Dettli et al[2] and Wagner[9])*

Drug	*a*	*b*	*Normal K%*	*Normal t½*
Ampicillin	11.0	.59	70	1.0
Carbenicillin	6.0	.54	60	1.2
Cephalexin	3.0	.67	70	1.0
Cephalothin	6.0	1.34	140	.5
Chloramphenicol	20.0	.10	30	2.3
Colistin	8.0	.23	31	2.2
Doxycycline	3.0	0	3	23.0
Erythromycin	13.0	.37	50	1.4
5-fluorocytosine	.7	.24	25	2.8
Gentamicin	2.0	.28	30	2.3
Kanamycin	1.0	.24	25	2.75
Lincomycin	6.0	.09	15	4.6
Methicillin	17.0	1.23	140	.5
Oxacillin	35.0	1.05	140	.5
Penicillin G	3.0	1.37	140	.5
Streptomycin	1.0	.26	27	2.6
Sulfamethoxasole	7.0	0	7	9.9
Tetracycline	.8	.07	8	8.7
Trimethoprim	2.0	.04	6	12.0
Vancomycin	.3	.12	12	5.8

a = percent hourly loss due to nonrenal processes
b = slope of the line
K% = the overall rate constant for elimination of the drug from the body as a percent per hour
t½ = half-life

body weight will achieve a peak level within this range. Since t½ is serum creatinine times three, and the dose is given every third t½, the dosage interval in renal failure is nine times serum creatinine.[11] Serum creatinine must be stable to apply this formula—that is, dosage for a 70-kg man with serum creatinine of 3.0 would be calculated as 7×70, or 490 mg every 27 hours (3×9). Since 50 percent of dose is removed by dialysis, 3.5 mg per kg of body weight should be supplemented after the average dialysis.

For gentamicin, the t½ in hours equals four times serum creatinine. Normal dosage interval is eight hours—every third t½. (The usual interval of eight hours probably results in drug levels which are subtherapeutic for considerable times, and the drug would more properly be given every four hours or every six hours.) Therapeutic serum level is 4 to 10 μg per ml, and a loading dose of 2 to 3 mg per kg will achieve a peak level in this range. Since t½ is serum creatinine times four, and one should give the drug every second t½, the dosage interval in renal failure should be the serum creatinine times eight[12] (that is, a 70-kg man with serum creatinine of 3.0 would get 140 mg [2×70] every [3×8] 24 hours). Since 75 to 100 percent of dose is removed by dialysis, 1 mg per kg of body weight should be supplemented after the average dialysis.

Because of the considerable interval during which subtherapeutic concentrations of drug exist using fixed interval therapy,[13] a compromise approach might be 2 to 3 mg per kg load and 1 mg per kg every t½; or the method which we prefer, 2 mg per kg and .4 mg per kg at intervals of two times the serum creatinine in hours. Blood levels should be used to monitor therapy one hour after a dose for peak levels (should be <12 μg per ml) or before the next dose for trough levels (should be >2 μg per ml). In critically ill patients, gentamicin can be given by continuous intravenous infusion.[14] The infusion rate in mg per minute is equal to ten times serum level desired divided by the t½ in minutes.

For antibiotic drugs where less than 15 percent of the drug appears unchanged in the urine, no dosage modification for renal failure is necessary.[13] Examples of these would include lincomycin, clindamycin, isoniazid and doxycycline. Chloromycetin is not primarily handled by renal excretion, although antibacterially inactive metabolites are renally excreted. These metabolites may cause marrow toxicity when they accumulate.

Some antibiotic drugs with major renal excretion do not need dosage modification because, although blood levels may increase notably, the results of such increase are usually clinically insignificant.[14] These in general include penicillins, cephalosporins and sulfonamides. Extremely high drug levels of penicillins may cause coagulopathy and hypokalemic metabolic alkalosis and seizures in patients with renal failure.[15-17] Cephaloridine, unlike other cephalosporins, causes nephrotoxic reactions in doses greater than 4 grams per day. These are manifested as proximal tubular necrosis and the drug should be carefully adjusted in patients with renal disease.

Some antibiotics should be avoided in renal failure.[18] A nitrofurantoin metabolite can accumulate and cause peripheral neuritis if the GFR is less than 20 ml per minute. The tetracycline group, except doxycycline, are antianabolic agents and therefore promote azotemia and acidosis.

Cardiac Glycosides

For cardiac glycosides it is customary to reduce the dosage and give the drug at the usual daily dosage interval. Jelliffe[19] computed the t½ of digoxin in subjects with normal renal function and found it to be 1.6 days. Therefore, in the usual 24-hour dosing interval 35 percent of the total amount of drug in the body was lost. Patients who were anuric had t½ of 4.4 days and lost 14 percent of their digoxin stores per day. The 14 percent presumably represents extrarenal metabolism. If the total body stores are known (V_D), then the daily maintenance dose should be 14 percent of the stores or loading dose, plus an additional percentage of body stores to replace urinary losses. The daily urinary losses are proportional to the creatinine clearance. Since about 20 percent of the body's digoxin stores are lost daily by renal excretion at a creatinine clearance of 100 ml per minute, approximately 10 percent will be lost if the clearance is 50 ml per minute, 5 percent if the clearance is 25 ml per minute and so forth. This percentage added to the 14 percent nonrenal losses should give the correct maintenance dose. If the digitalizing dose is not known, the body stores can be estimated from the serum digoxin level and the V_D which is 7.3 liters per kg of lean body weight by the formula $7.3 \text{ (weight in kg)} = \frac{\text{body stores}}{\text{serum level}}$.[20] For digitalizing patients with renal failure, most clinicians

give the usual or only slightly reduced loading doses of digoxin.[21] It should be noted that with a change in the maintenance dose a new steady state is not reached for approximately four times t½. Digoxin is not appreciably dialyzed clinically.

Digitoxin is mainly eliminated from the body by nonrenal routes. Renal failure therefore has much less effect in altering digitoxin kinetics.[22] The t½ in patients with normal renal function is six days, which corresponds to a daily percent loss of 11 percent of body stores. An anuric patient has a t½ of 8.5 days and loses 8 percent of body stores daily. It is of interest that about 8 percent of daily digitoxin losses are due to conversion to digoxin by the liver. Thus, digitoxin dosage schedules, although theoretically needing minor alterations in renal failure, need not be too different from usual therapy. The maintenance dose for renal failure expressed as percentage of usual dose is 63 percent for anuric patients, 79 percent if Cl_{Cr} is 50 ml per minute and 86 percent if Cl_{Cr} is 75 ml per minute.[22]

Drug-Drug Interactions

Clinically, the problem of therapy in renal disease is complicated by the necessity for multiple therapy and possible drug-drug interactions. These can result in enzyme inductions or inhibitions in hepatic drug metabolizing enzymes. Drugs may displace other drugs from receptors at sites of action decreasing the effect of the displaced drug, or, conversely, drugs may displace other drugs from plasma proteins increasing pharmacologic action of the displaced drug. Finally, one drug may influence the renal excretion or intestinal absorption of another agent. A discussion of drug interactions in renal disease has been published recently.[23]

Dialysis of Drugs and Poisons

Generalizations can be made regarding the potential value of dialysis in the management of poisoning or need to adjust dosage for loss of therapeutic efficacy due to dialysis losses. First, the drug should diffuse through dialysis membrane in significant amounts. Second, a significant quantity of substance should be in plasma water and thus presumably accessible for diffusion. Finally, to be useful in poisoning, toxic effects should relate to plasma concentration and duration of the drug in body, and the amount dialyzed should be a significant addition to amount of drug elimination by other means.

A list of drugs where dialysis may be useful for poisonings is shown in Table 5.

Drugs which should be supplemented to replace dialysis losses and general guidelines for therapy with common drugs in patients with renal insufficiency are available in several recent references.[18,24,25]

TABLE 5.—*Well-established Indications for Dialysis of Overdoses*

Drug	*Indication*
Methyl alcohol	Blood level >50 mg per 100 ml
Ethyl alcohol	Blood level >300 mg per 100 ml
Phenobarbital	Blood level >20 mg per 100 ml
Carbon tetrachloride.	Within 1st 48 hours after ingestion
Ethylene glycol	Within 1st 48 hours after ingestion
Aspirin	Blood level >90 mg per 100 ml

REFERENCES

1. Gibaldi M, Perrier D: Drug distribution and renal failure. J Clin Pharm 12:201-204, 1972
2. Dettli L, Spring P, Ryter S: Multiple dose kinetics and drug dosage in patients with kidney disease. Acta Pharmacol (Kbh) 29 (Suppl 3):211-224, 1971
3. Reidenberg MM: Kidney disease and drug metabolism. Med Clin N Amer 58:1059-1062, 1974
4. Letteri JM, Mellk H, Louis S, et al: Diphenylhydantoin metabolism in uremia. N Engl J Med 285:648-652, 1971
5. Englert E, Brown H, Willarson DG, et al: Metabolism of free and conjugated 17-hydroxycorticosteroids in subjects with uremia. J Clin End 18:36-43, 1958
6. Reidenberg MM, Affrime M: Influence of disease on binding of drugs to plasma proteins. Ann N Y Acad Sci 226:115-126, 1973
7. Koch-Weser J: Serum drug concentrations as therapeutic guides. N Engl J Med 287:227-231, 1972
8. Orr JS, Shimmins J, Spiers CF: Method for estimating individual drug dosage regimens—An application of the occupancy principle. Lancet 2:771, 1971
9. Wagner JG: Relevant pharmacokinetics of antimicrobial drugs. Med Clin N Amer 58:479-492, 1974
10. Kunin CM: Antibiotic usage in patients with renal impairment. Hospital Pract 7:141-149, 1972
11. Cutler RE, Orme BM: Correlation of serum creatinine concentration and kanamycin half-life. Therapeutic implications. JAMA 209:539-542, 1969
12. McHenry MC, Gavan TL, Gifford RW, et al: Gentamicin dosages for renal insufficiency—Adjustments based on endogenous creatinine clearance and serum creatinine concentration. Ann Intern Med 74:192-197, 1971
13. O'Grady F: Antibiotics in renal failure. Br Bull Med 27: 142-147, 1971
14. O'Grady F, Brown WRL, Gaya H, et al: Antibiotic levels on continuous IV infusion. Lancet 2:209, 1971
15. New PS, Wells CE: Cerebral toxicity associated with massive intravenous penicillin therapy. Neurology 15:1053-1058, 1965
16. Bloomer HA, Barton LJ, Maddock RK: Penicillin induced encephalopathy in uremic patients. JAMA 200:121-123, 1967
17. Brunner FP, Frick PG: Hypokalemic metabolic alkalosis and hypernatremia due to massive sodium penicillin therapy. Br Med J 4:550-552, 1968
18. Whelton A: Antibacterial chemotherapy in renal insufficiency. Antibiot & Chemother 18:1-48, 1974
19. Jelliffe RW: An improved method of digoxin therapy. Ann Intern Med 69:703-717, 1968
20. Jusko WJ, Szefler SJ, Goldfarb AL: Pharmacokinetic design of digoxin dosage regimens in relation to renal function. J Clin Pharm 14:525-535, 1974
21. Jelliffe RW, Brooker G: A nomogram for digoxin therapy. Amer J Med 57:63-68, 1974
22. Jelliffe RW, Buell J, Kalaba R, et al: An improved method of digitoxin therapy. Ann Intern Med 72:453-464, 1970
23. Melmon K, Morelli J (Eds): Clinical Pharmacology. Macmillan, New York, 1972
24. Reidenberg M: Renal Function and Drug Action. Saunders, Philadelphia, London, Toronto, 1971
25. Bennett WM, Singer I, Coggins CJ: A guide to drug therapy in renal failure. JAMA 230:1544-1553, 1974

Refer to: Methicillin induced interstitial nephritis—Medical Staff Conference, University of California, San Francisco. West J Med 123:380-385, Nov 1975

Methicillin Induced Interstitial Nephritis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *This morning the topic for Medical Grand Rounds is methicillin induced interstitial nephritis. Dr. Barry Zacherle from the Division of Nephrology will discuss the topic and a patient recently seen on the Medical Service will be presented by Dr. McCurley.*

DR. MCCURLEY:† A 73-year-old white woman was admitted to the University of California Medical Center with exfoliative erythroderma. Twelve days before admission an erythematous papular rash developed on her chest. During the week before admission the rash became generalized, her skin became edematous and fever, chills and malaise were present. There had been similar episodes of generalized erythroderma at 3 to 4 year intervals since age 16. On physical examination, the patient appeared to be acutely ill. The pulse was 90 beats per minute, temperature 36.9°C (98.4°F) and blood pressure 150/72 mm of mercury. The skin was diffusely erythematous and scaly on face, trunk and extremities, and there was generalized edema which was nonpitting. A grade II/VI systolic murmur at the left lower sternal border was noted. The admission laboratory data were pertinent as follows: hematocrit was 39.1 percent, leukocyte count was 16,500 per cu mm; the differential was 51 polymorphonuclear cells, 6 banded cells, 6 eosinophils and 37 percent lymphocytes. The peripheral smear had toxic granulation and vacuolation of the polymorphonuclear leukocytes. The serum creatinine was 1.1 mg per dl with blood urea nitrogen of 18 mg per dl. Findings on urinalysis showed no protein, 4 to 5 leukocytes and no red cells per high-power field.

The exfoliative erythoderma resolved after a seven-day course of high dose parenteral and topical steroids. Five of nine blood cultures drawn after admission grew Staphylococcus aureus and on December 26, 1974, the patient was started on 8 grams per day of methicillin. Fourteen days later the patient had a hard-shaking chill associated with a temperature of 39°C (102.2°F). Findings on urinalysis showed no protein, 4 to 5 leukocytes per high-power field and no red cells. Serum creatinine was 1 mg per dl. Fever continued, and three days later serum creatinine was 6.9 mg per dl with 8 percent eosinophils on dif-

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Thomas McCurley, MD, Intern in Medicine.

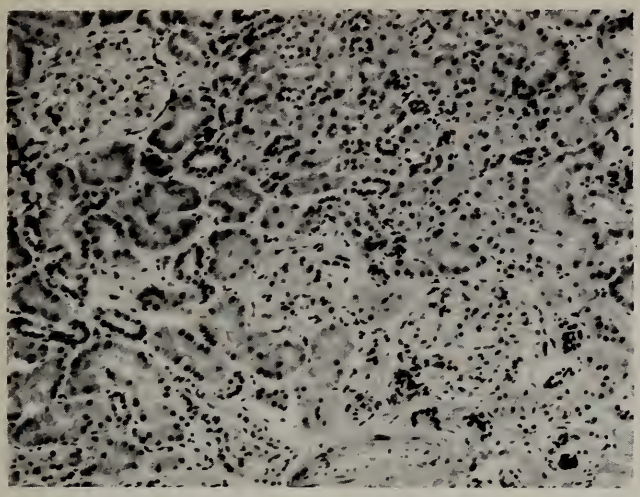


Figure 1.—Section of a biopsy specimen of a normal kidney.

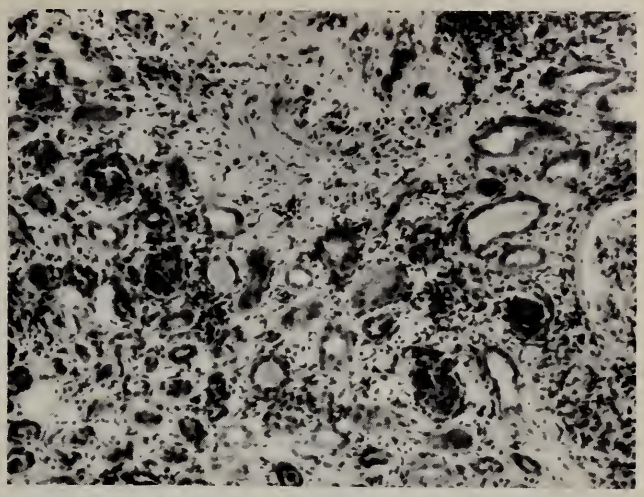


Figure 2.—Section of a kidney biopsy specimen from patient with methicillin interstitial nephritis.

ferential leukocyte cell count. On testing, urine had 3 + proteinuria, 1 to 3 tubular epithelial cells per high-power field and 4 to 5 red blood cells per high-power field. Findings on intravenous pyelogram and renal scan showed bilaterally poorly functioning kidneys without obstruction. Serum complement levels were normal. A renal biopsy specimen was taken, the histology of which showed an interstitial nephritis.

Treatment with parenteral steroids was begun and after one week the creatinine level had fallen to 2.1 mg per dl. Steroids were discontinued and creatinine rose to 4.6 mg per dl. At that time there were 16 percent eosinophils on differential count and results of urinalysis showed 1 + proteinuria with 3 to 5 tubular epithelial cells and 1 to 2 red cells per high-power field. Administration of prednisone (40 mg per day) was begun again and four days later the serum creatinine level was 2.6 mg per dl.

Dr. Zacherle:* In the patient presented this morning, acute renal failure was present due to an interstitial nephritis which appeared to be secondary to methicillin. Today I would like to discuss interstitial nephritis in general with the emphasis on drug-induced acute interstitial nephritides, particularly methicillin nephritis. The latter is the interstitial nephritis with which we are most apt to be confronted clinically today.

Interstitial nephritis is primarily a histologic diagnosis. Figure 1 shows a section of a normal kidney biopsy specimen. The glomeruli are normal with open capillary loops, thin lacey capillary basement membranes and a normal amount of mesangial substance and cellularity. The tubules are plentiful, filling up most of the remaining space, and appear normal. Those vessels present are also normal. The interstitial substance located between the glomeruli, tubules and vessels is essentially inapparent; this is the normal histology. Interstitial nephritis is, as the name implies, an inflammation of the interstitium without much change in the other structures (glomeruli, tubules or vessels). The interstitium becomes prominent; in the acute situation this is due to edema, but if the process becomes more chronic, fibrosis occurs. There is also a cellular inflammatory response which usually consists of polymorphonuclear leukocytes acutely and round cell infiltration later. Figure 2 is a section from the kidney biopsy specimen in the case under discussion today. The interstitial material is very apparent and there is an active cellular inflammatory response which is particularly prominent around the tubules. Although not apparent in this picture, many of the inflammatory cells are eosinophils.

Clinically, as well as histologically, interstitial nephritis may be categorized as acute or chronic. Table 1 lists several of the systemic illnesses associated with both types. Although chronic disease is usually indolent and slowly progressive in its course, acute nephritis is more apt to be associated with an acute illness and a rapid deterioration of renal function. Before the introduction of antibiotics this was most commonly seen in children with acute febrile illnesses, particularly scarlet fever and diphtheria. Currently it is occasionally seen associated with leptospirosis and brucellosis, but that which we are most likely to see as

*Barry Zacherle, MD, Assistant Clinical Professor of Medicine and of Ambulatory and Community Medicine.

practicing physicians in 1975 is acute interstitial nephritis associated with a drug reaction.

The first descriptions of such drug reactions involved the sulfonamides. In the early 1940's drug reactions to the sulfonamide antibiotics were described and included glomerulonephritis, vasculitis and interstitial nephritis. The same changes have been reported as reactions to other drugs such as the anticoagulant phenindione, diphenylhydantoin and more recently, methicillin, penicillin and ampicillin. In 1973, Lyons and coworkers[1] suggested that the same clinical features might occur also with thiazide diuretics. The latter is not surprising because the thiazides are chemically related to the sulfonamide drugs.

The first reports of methicillin associated renal disease appeared in the early 1960's. Sporadic case reports then appeared throughout the mid 1960's, and in 1968 Baldwin and his associates[2] compiled the cases of seven patients who had been receiving either methicillin or penicillin G, or both, and who had fairly distinct clinical features associated with acute interstitial nephritis noted on kidney biopsy. In the typical clinical presentation, fever is usually the first sign noted and then eosinophilia with or without rash appears. Subsequently the renal manifestations appear, although this sequence somewhat is variable. In fact, Baldwin had one patient in his group of seven in whom fever did not develop until after renal insufficiency was already present. In most of the cases reported in the literature the systemic manifestations are followed variably by hematuria, pyuria proteinuria and renal insufficiency, and on kidney biopsy an acute interstitial nephritis is seen. This renal insufficiency is usually of a moderate degree, and recovery usually follows cessation of the administration of the antibiotic.

TABLE 1.—*Interstitial Nephritides*

ACUTE
Infections
Scarlet fever
Diphtheria
Leptospirosis
Brucellosis
Drugs
Sulfonamides
Phenindione
Diphenylhydantoin
Methicillin-penicillin-ampicillin-thiazides-furosemide
CHRONIC
Pyelonephritis
Analgesic abuse
Ischemia
Radiation
Balkan nephritis
Sarcoid
Lead
Sjögren's syndrome

Figure 3 shows the pertinent features of the case presented today. The patient was admitted with erythroderma, and because there was exfoliation, administration of prednisone was begun promptly. Eosinophilia was present when the patient came into the hospital, and there was no fever. The erythroderma cleared rapidly when the patient was taking prednisone and the dosage of prednisone was tapered shortly after admission. Results of three separate sets of blood cultures were positive for penicillin-resistant Staphylococcus aureus and she was begun on intravenous methicillin, 8 gm per day. The blood cultures were subsequently negative for S. aureus. The patient remained afebrile, serum creatinine ranged between 0.9 and 1 mg per dl and urine output was appropriate for fluid intake. Body weight did not change appreciably during the entire course of the time spent in hospital.

After two weeks of methicillin therapy it was discontinued and oral administration of dicloxacillin was begun as indicated in Figure 3. During that period, the erythroderma flared slightly and fever developed. On the third day of that febrile episode, administration of methicillin was again begun and there were two days of both methicillin and dicloxacillin therapy. On the third day of that febrile episode it was noted that the serum creatinine level had risen to 6.9 and the patient was anuric. At this juncture, the usual features of methicillin nephritis appear to have been present—except for the anuria, which is unusual. With the possibility of vasculitis in mind, administration of prednisone was begun again and a renal biopsy specimen was obtained. When the renal biopsy specimen was examined and showed a typical interstitial nephritis, the prednisone was discontinued. During that period, urine output increased, renal function improved and serum creatinine fell to a level of 2.1 mg per dl. The patient became afebrile very quickly.

A week after the prednisone was discontinued, there was a spiking temperature and the serum creatinine level rose again to almost 5 mg per dl. The patient was extensively evaluated at this point for any other cause of renal insufficiency and none was found. Administration of prednisone

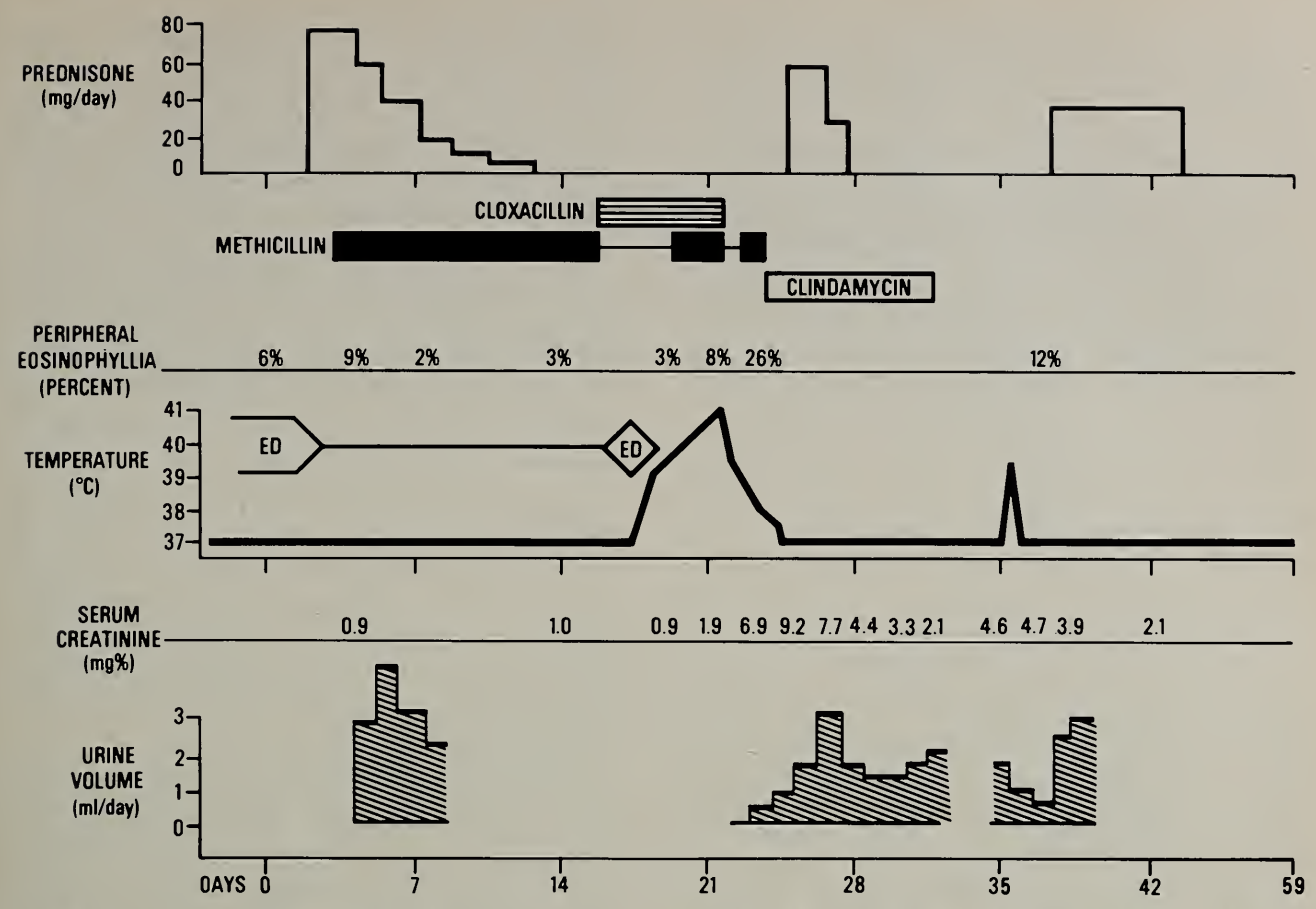


Figure 3.—Clinical course of patient with methicillin interstitial nephritis. ED is an abbreviation used for erythroderma.

was started again and serum creatinine, which may have begun to decrease before the prednisone therapy was begun, fell to 2.1 mg per dl.

Most of the features of typical methicillin interstitial nephritis were present in this patient. There are several peculiarities, however, that merit special attention. One is the extreme degree of renal insufficiency. The second is that although the methicillin was discontinued and the renal function did improve initially, it deteriorated again later. The third is the question of what role prednisone may have had in the waxing and waning course of renal function in the patient.

There are 24 cases of methicillin-associated interstitial nephritis in the literature. In four of the patients there was severe renal insufficiency; in the rest the usual features of only moderate renal insufficienty were seen. One case has been reported[3] in which the patient was anuric. Therefore, although the usual feature is mild or moderate renal insufficiency, in approximately 15 percent of the cases very severe renal insufficiency and even anuria may develop. Second, what about the cessation of methicillin? It is very clear in the literature that, in most of the cases, the patients do get better. However, there is one well-documented case in which the patient's renal function continued to deteriorate for several weeks following the cessation of penicillin and methicillin; this is also the only recorded case in the literature in which there was a clear response in the patient to steroid administration. The degree of ultimate recovery of function has not been carefully evaluated. In at least three patients, there was significant, persistent renal insufficiency. So, although recovery is usual, it may not always follow cessation of the antibiotic administration and may be significantly incomplete. Finally, among 24 of the previously reported patients, only three have been treated with steroids. In one[5] there was an immediate improvement in the eosinophilia and fever and no change in renal function. In another[3] there was an immediate improvement in renal function; however, administration of prednisone was begun at the same time that methicillin was discontinued. In the third case,[4] clear-cut response to steroid therapy occurred on two occasions during the patient's course.

Steroid therapy also appears to have been help-

ful in the treatment of acute interstitial nephritis associated with thiazide administration. Lyons and co-workers[1] described a group of four patients who had nephrotic syndrome. Findings from renal biopsies done during the course of evaluation of nephrotic syndrome showed glomerular disease with very little interstitial involvement. These patients were all treated with a number of medications including thiazide diuretics and furosemide, and over a course of several months there was pronounced deterioration of renal function in all of them. Of these four patients, two had peripheral eosinophilia, and two did not. Biopsy studies were done again and at that point pronounced acute interstitial nephritis was noted. Those four patents were treated with steroids and in all a significant clinical response was obtained over a short length of time.

If drug-induced interstitial nephritis is a distinct entity, why does it occur and what is the pathophysiology? The pathogenesis is not understood, but it is probably an immunologic disease. This was first suggested by the clinical features which include rash, eosinophilia and fever. There are two patients in the literature who have been carefully evaluated from an immunological standpoint, one patient in Baldwin's study[2] and another patient described by Border and his associates[5] in 1974. Both of these investigators made antibody to a dimethoxyphenyl penicilloyl moeity which is the haptenic or antigenic portion of methicillin. With that antibody to methicillin they were able to show staining of kidney basement membranes of their patients. In one case staining was found only on tubular basement membrane, and in the other case it was found on both tubular and glomerular basement membrane. This staining was shown to be very specific for the methicillin antigen; the authors were unable to obtain similar staining in tissue from normal persons, or from patients with other renal diseases. Antiserum against the benzylpenicilloyl moeity, the antigen of penicillin G, did not cause staining. Furthermore, both authors were able to block staining by absorption with methicillin, methicillin coated red cells or the univalent dimethoxyphenyl penicilloyl moeity. So it appears that in both, an antigenic portion of the methicillin molecule could be detected on at least the tubular basement membrane. Border[5] was also able to find a circulating factor in the serum of his patient which indirectly stained normal human or monkey basement membrane. This staining could be blocked by absorption against human tubular basement membrane, but not against methicillin or methicillin coated red cells. Thus, it appeared that this factor in the serum was directed at the tubular basement membrane and not the methicillin.

Steblay and Rudofsky[6] produced in rabbits an antiserum against renal tubular basement membrane which they were able to inject into guinea pigs and produce not only staining of the tubular basement membrane but also an active interstitial nephritis. This animal model may or may not be analogous to the human disease. Border and coworkers[5] were unable to produce interstitial nephritis in monkeys by injecting them with the antibasement membrane factor from their patient, in spite of their ability to detect by fluorescent staining the presence of basement membrane factor in the tubules. They postulate that this may have been due to the lower antibody titer in their own preparation.

Although the experimental, immunologic data are not entirely clear, they do offer suggestions as do the clinical data, and a hypothesis regarding pathogenesis can be formulated with which most of our information fits. In some patients who for unknown reasons are susceptible, a portion of the methicillin molecule is bound to tubular basement membrane protein. Penicillin, methicillin and ampicillin are all organic acids and are secreted by the proximal tubular epithelial cells. It is of interest that the thiazides are also organic acids and are secreted in the same location by the same mechanism. The tubular basement membrane-methicillin complex thus formed may then act as an immunogen which stimulates the production of an immunoglobulin G (IgG) antibody directed against the tubular basement membrane. The resulting tissue response to the subsequent antigen-antibody reaction is an interstitial nephritis.

In conclusion, interstitial nephritis may occur as an acute illness, and in most of our clinical practices it will appear as a reaction to a drug. This reaction is probably mediated by a series of immunologic events. The usual clinical presentation of this entity is well described, and most cases fit into the pattern described. However, it is now apparent that there are clinically important variations from this usual course. In approximately 15 percent of cases, patients may experience profound renal insufficiency, even anuria. It is also clear that although interstitial nephritis usually improves when the offending drug or

agent is discontinued, rarely it may continue to progress. Furthermore, although renal function usually returns, in a small fraction of instances there may be significant residual renal damage.

The role of corticosteroid therapy in this disease has not been clarified. However, in view of the data available and the occasional poor prognosis of the underlying illness, there may be at least some cases of acute interstitial nephritis in which glucocorticosteroid therapy will be beneficial and necessary for optimal recovery.

REFERENCES

1. Lyons H, Pinn VW, Cortell S, et al: Allergic interstitial nephritis causing reversible renal failure in four patients with idiopathic nephrotic syndrome. N Engl J Med 288:124-128, Jan 18, 1973

2. Baldwin DS, Levine BB, McCluskey RT, et al: Renal failure and interstitial nephritis due to penicillin and methicillin. N Engl J Med 279:1245-1252, Dec 5, 1968

3. Simenhoff ML, Guild WR, Dammin GJ: Acute diffuse interstitial nephritis. Am J Med 44:618-625, Apr 1968

4. Gilbert DN, Gourley R, d'Agostino A, et al: Interstitial nephritis due to methicillin, penicillin and ampicillin. Ann Allergy 28:378-385, 1970

5. Border WA, Lehman DH, Egan JD, et al: Antitubular basement-membrane antibodies in methicillin associated interstitial nephritis. N Engl J Med 291:381-384, Aug 22, 1974

6. Steblay RW, Rudofsky V: Transfer of experimental autoimmune renal cortical tubular and interstitial disease in guinea pigs by serum. Science 180:966-968, 1973

Clomiphene (Clomid®): Is it Teratogenic?

The advantages of using clomiphene citrate far outweigh the possible disadvantages of using the drug . . . It is much safer to treat patients who have problems with anovulation as the cause of their infertility with clomiphene than to use the other agent that is available—human menopausal gonadotropin. Clomiphene citrate is a safe drug. Those ten percent of patients who have anovulation or oligo-ovulation as the cause of their infertility have a high chance of conceiving with treatment with clomiphene citrate. And if it is used correctly, with the pelvic examination done before each treatment, of course, there is no increased incidence of congenital abnormalities of the babies. Of course, a physician should take special precautions by doing a pelvic examination insuring the patient is not pregnant before each treatment course. And legally, the patient should be informed as to the possibility of multiple births. Other than these, physicians should continue to use clomiphene for the treatment of those infertility patients who do not ovulate or ovulate infrequently. They should not use the drug in the treatment of infertility patients in whom there are other causes for infertility.

In our clinic, we have been using clomiphene citrate at higher than the recommended dosage—higher than 100 mg per day for five days. We have treated patients with as much as 250 mg per day for five days. At the higher dosages, some of the patients have conceived where they have not ovulated or conceived at the lower dosages. In our series of 24 babies born with treatment with this graduated sequential increasing medication regime of clomiphene citrate, we have had only one of the babies born with congenital abnormalities—a congenital heart defect—and in this case the recommended dosage of 50 mg per day for five days was given. Therefore, it is my opinion that clomiphene continues to be a safe drug and is extremely useful for a patient with infertility who does not ovulate. Physicians do not have to be concerned about teratogenic effects of this agent.

—DANIEL R. MISHELL, JR., MD, *Los Angeles*

Extracted from *Audio-Digest Obstetrics and Gynecology,* Vol. 21, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angees, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—Nuclear Medicine

The Scientific Board of the California Medical Association presents the lowing inventory of items of progress in Nuclear Medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Nuclear Medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

The Current Status of Indium-111 Labeled Bleomycin for Tumor Detection

BLEOMYCIN IS A mixture of closely related polypeptides that have antineoplastic and antibiotic properties. Tritiated preparations of bleomycin are localized preferentially in certain types of tumors. Since bleomycin also has the properties of a chelating agent, it can be labeled with radioactive metals. It has been actively investigated as a tumor imaging agent. Most of the work that has been done with this agent in the United States has been accomplished with the ^{111}indium (^{111}In) labeled form of bleomycin. Unfortunately, transferrin, present in the plasma, competes with bleomycin for the ^{111}In label and as a result tends to leech label from the bleomycin when it is injected parenterally. The ^{111}In bound to the transferrin is then deposited in bone marrow, liver, spleen, kidneys and bladder resulting in significant background activity in the scan. The chief potential advantage of ^{111}In labeled bleomycin over other tumor scanning agents is the fact that it does not deposit in the normal bowel, therefore it is potentially useful for detecting intraabdominal disease. Although good clinical results have been described with use of ^{111}In bleomycin for tumor detection and staging, its relative status compared with gallium-67 (^{67}Ga) citrate is still somewhat controversial. Localization of ^{111}In bleomycin has also been reported in abscesses and other inflammatory lesions although no large series has yet been published comparing it with ^{67}Ga for abscess detection.

^{111}Indium bleomycin does localize in human tumors. Its role in tumor detection and staging as compared with ^{67}Ga is still somewhat controversial.

RONALD D. TAYLOR, MD
W. H. BLAHD, MD

REFERENCES

Groves RB, Reba RC, Eckelman WC, et al: Clinical evaluation of radiolabeled bleomycin (Bleo) for tumor detection. J Nucl Med 15:386-395, Jun 1974

Lilien DL, Jones SE, O'Mara RE, et al: Clinical evaluation of ^{111}In-bleomycin. J Nucl Med 15:512, Jun 1974

Cerebral Flow Studies Done with Brain Scan

THE RADIOACTIVE TRACERS normally used in static brain scanning do not cross the intact blood brain barrier; they distribute in the venous pool and extracellular spaces (that is, not normally in the brain substance). They nonspecifically delineate any abnormality that causes blood brain barrier breakdown by accumulating in the brain substance. The one most commonly used is ^{99m}-technetium (^{99m}Tc) pertechnetate. Most supratentorial and posterior fossa tumors, cerebrovascular accidents at least several days after clinical onset and chronic subdural hematoma are well delineated with this technique.

Cerebral flow studies have been shown to enhance brain scanning by adding a hemodynamic evaluation. This procedure is often referred to as cerebral radionuclide angiography (CRAG). The study employs the same radiopharmaceutical dose administered for the subsequent brain scan. The dose is injected rapidly into a large peripheral vein with the patient's head placed either directly in front of a scintillation camera to view both neck and cranial vasculature or only the cranial vasculature in a vertex projection.

The dynamics of radioactivity distribution can be depicted by multiple, sequential polaroid film images made approximately every two or three seconds following injection. Alternatively, more elaborate processing of data can be done with a minicomputer data analysis system to assess objectively the vascular asymmetry. Because nondiffusible tracers are used, no absolute measurements (such as ml per gram per minute) of flow are determined.

From the clinical diagnostic standpoint six useful patterns of this flow study can be observed: (1) an abrupt intracranial "hot spot," at the onset of the arterial phase, which rapidly fades—arteriovenous malformation; (2) slightly less abrupt "hot spot" that persists well into the venous phase—meningioma; (3) focally decreased area in the internal or common carotid artery with symmetrical activity in the middle cerebral artery (MCA) distributions—extracranial vascular occlusion with adequately functioning circle of Willis; (4) decreased activity in one MCA area that subsequently does not fill in—intracerebral tumor or hematoma; (5) decreased activity in one MCA area that subsequently fills in either due to prolonged transit time or to collateral flow—cerebral vascular accident (frequently seen *before* the brain scan becomes "positive"), and (6) decreased activity along one or both cerebral convexities—subdural hematoma (seen with acute subdural even *before* the brain scan becomes "positive").

J. MICHAEL USZLER, MD

REFERENCES

Cowan RJ, Maynard CD, Meschan I, et al: Value of the routine use of the cerebral dynamic radioisotope study. Radiology 107:111-116, Apr 1973

Deland FH: The brain, chap 8, *In* Nuclear Medicine. New York, HP Publishing Co., Inc., 1975, pp 84-93

Wagner HN Jr: Cerebral circulation, chap 9, *In* Wagner HN Jr, Block I (Eds): Nuclear Medicine. New York, Hospital Practice Publishing Co., Inc., 1975, pp 94-102

Thyroid Cancer Following Juvenile Neck Irradiation

—A New Role for Thyroid Imaging

IN 1973, DEGROOT AND PALOYAN reported "a Chicago endemic" of postirradiation thyroid cancer. The report had some disturbing disclosures, including the fact that in 20 percent of their patients with malignant tumors findings were normal on isotope thyroid scans. They found the isotope scan of minor utility and suggested that any palpable nodule should be considered suspect in a patient with history of thyroid irradiation, even if the nodule was not detectable on scan.

Now, Arnold and co-workers report that in patients with a history of neck irradiation, *nonpalpable cold nodules can be detected by radionuclide imaging*. These nodules have about a 20 percent probability of maligancy. Arnold studied a large group of patients (almost 1,500) whose primary reason for referral was a history of childhood neck irradiation and he used radioactive technetium (^{99m}Tc) pertechnetate in combination with a gamma camera to produce very high resolution thyroid images. Arnold's findings destroy another common concept about thyroid cancer. In the irradiated group, the incidence of malignancy in patients with multiple nodules (39 percent) was virtually the same as in patients with single "cold" nodules (33 percent).

Traditionally, virtually all thyroid cancer was thought to present as isotopically cold nodules, and the value of an isotope scan was to confirm that the palpable nodule was cold and solitary. Multiple nodules were felt to be a sign of be-

nignity. These concepts are now under vigorous attack.

Many forms of thyroid cancer have a relatively benign clinical course even if untreated, and there is still enough controversy regarding the pathologic differentiation of benign from malignant tumors to provide traditionalists with ammunition to defend older attitudes. To date no patient who has had thyroid cancer detected as a result of postirradiation screening tests has died of the disease. However, the most conservative approach is to treat many of the classic concepts about thyroid cancer with skepticism, especially in patients who have received radiation in childhood. Palpation, scintiphotographs and thyroid function tests are indicated in all persons with history of such irradiation. Either a palpable nodule *or* nonpalpable "cold" area on scintiphoto is sufficient indication to at least consider surgical operation. If all thyroid studies give normal findings, treatment with replacement doses of thyroxine may provide some protection against future tumor development.

PAUL B. HOFFER, MD
MICHAEL OKERLUND, MD

REFERENCES

DeGroot L, Paloyan E: Thyroid carcinoma and radiation—A Chicago endemic. JAMA 225:487-491, Jul 30, 1975

Arnold J, Pinsky S, Ryo UY, et al: ^{99m}Tc-pertechnetate thyroid scintigraphy in patients predisposed to thyroid neoplasms by prior radiotherapy to the head and neck. Radiology 115:653-657, Jun 1975

Abnormal Brain Scan Findings Resulting from Prior Electroencephalograms

A BRAIN SCAN and an electroencephalogram are used often in combination to evaluate patients with neurologic symptoms. When these two modalities are required, the brain scan should be done first.

Much of the cranial activity seen on a brain scan results from radionuclide accumulation in the extracellular fluid of the scalp and skull. The minimal scalp irritation associated with the application of electroencephalographic electrodes with electrode glue has been reported to result in a local increase in extracellular fluid concentration and a corresponding increase in activity on the brain scan. In the preceding twelve months at the University of California, San Diego, we have also observed abnormal brain scan findings following an electroencephalogram. The sites of abnormal accumulation were located peripherally and repeat scans several days later gave normal findings.

In summary, because an electroencephalogram may result in minor scalp trauma and localized radionuclide accumulation, a brain scan should be carried out first. When an electroencephalogram is done before the brain scan, the nuclear medicine physician concerned should be made aware of the electroencephalogram and the brain scan should be delayed, if possible, at least 48 hours.

ANDREW TAYLOR, JR, MD

REFERENCES

Oldendorf WH: Distribution of various classes of radiolabeled tracers in plasma, scalp, and brain. J Nucl Med 13:681-685, Sep 1972

Burt RW: Brain scan abnormalities produced by electroencephalographic procedures. J Nucl Med 15:369-370, May 1974

Gallium-67 Tumor Imaging

SINCE 1969, scanning with gallium-67 as the citrate has gained wide use, although its acceptance as a routine test in nuclear medicine is still limited because of the variability of uptake in bowel, liver, spleen and bone marrow and the nonspecificity of gallium for tumor.

In tumor evaluation gallium has found its greatest success in the detection and staging of lymphomas. The accuracy in detection of involved sites in Hodgkin's disease has been reported as 65 to 79 percent. The information from gallium scans and lymphangiograms is complementary. Efficacy above the diaphragm is better than below. Non-Hodgkin's lymphoma has a somewhat poorer detection rate and uptake seems to depend on the histocytic component.

Other tumors with high affinity to gallium citrate include bronchogenic carcinomas where mediastinal involvement may be detected while findings on x-ray studies are still normal. Melanoma detection has been evaluated in several institutions and found to be good in lesions larger than 2 cm. Gallium uptake in hepatoma may also be high with a reported detection rate of 70 to 90 percent.

Other tumors show greater variability in uptake even within tumor types. Adenocarcinomas are generally not well detected. Head and neck tumor evaluation has been moderately successful.

Twenty-five to 30 percent of these escaped detection (especially midline tumors).

A practical and useful application is the differential diagnosis of primary or metastatic brain tumors from cerebral infarcts since the latter are much less likely to concentrate gallium than tumors.

It is now generally recognized that gallium uptake is not tumor specific. Foci of inflammation will also show gallium accumulation. This uptake may be very rapid and pronounced. Therefore, gallium scanning has been useful in the search for occult infections.

Gallium scanning is no panacea for tumor detection but it is useful selectively to answer specific questions. Despite the pitfalls, valuable clinical information can be obtained in a noninvasive fashion and in special instances a gallium scan may be the *only* test of merit.

ALAN D. WAXMAN, MD
JAN K. SIEMSEN, MD

REFERENCES

Johnson GJ, Buena RS, Teates CD, et al: ^{67}Ga-citrate imaging in untreated Hodgkin's disease—Preliminary report of cooperative group. J Nucl Med 15:399-403, Jun 1974

Greenlaw RH, Weinstein MB, Brill AB, et al: ^{67}Ga-citrate imaging in untreated malignant lymphoma—Preliminary report on cooperative group. J Nucl Med 15:404-407, Jun 1974

Johnston GS, Jones AE: Atlas of Gallium-67 Scintigraphy. Plenum Press, New York-London, 1973

Noninvasive Radionuclide Imaging of Damaged Myocardial Tissue

DURING THE LAST two years, it has become apparent that imaging of damaged myocardial tissue, including acute myocardial infarcts, can be accomplished following an intravenous injection of an appropriate radionuclide. The technique, first described by Bonte and co-workers, utilizes an intravenous injection of 15 millicuries of radioactive technetium (^{99m}Tc) stannous pyrophosphate, a commonly used bone scanning agent. In a series of patient studies, ^{99m}Tc stannous pyrophosphate was clearly shown to localize in an area of acute myocardial infarction, the location of which correlated well with electrocardiogram (ECG) localization.

The mechanism of incorporation of the ^{99m}Tc stannous pyrophosphate into infarcted tissue is thought to be related to the presence of calcium phosphate crystals found within the mitochondria of irreversibly damaged myocardial cells.

Results of animal studies showed that an experimental infarct is imageable at approximately 12 to 16 hours after the infarct, with no change in localization of the radionuclide for up to six days following the infarct. Attempts to image after six days showed that the uptake of the radionuclide in the infarct began to fade and finally diasappeared. The radionuclide does not concentrate in old myocardial infarcts, so the technique might be useful in identifying superimposed acute infarction in a patient in whom findings are abnormal on an ECG. The eventual role that this procedure will play in the workup of suspected myocardial infarcts is still uncertain because the incidence of false positive and false negatives has not been established.

In addition to infarct imaging, other approaches to imaging the myocardium by radionuclide techniques are being studied. Thallium-201 is an example of another promising agent which localizes in normal myocardium but not in damaged myocardium. This agent does not distinguish between acute and chronic damage and therefore may play a complementary role to the ^{99m}Tc pyrophosphate scan. Potassium-43 and cesium-129 and rubidium-81 have been tested as indicators of myocardial perfusion but there are disadvantages to their use, such as high cost and relatively poor resolution images.

NAOMI ALAZRAKI, MD

REFERENCES

Bonte FJ, Parkey RW, Graham KD, et al: A new method for radionuclide imaging of myocardial infarcts. Radiology 110:473-474, Feb 1974

Parkey RW, Bonte FJ, Meter SL, et al: A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 50:540, Sep 1974

Wenzel WW, Heasty RG: Uptake of ^{99m}Tc-stannous polyphosphate in an area of cerebral infarction. J Nucl Med 15:207-209, Mar 1974

The Role of Inhalation Lung Scans in the Diagnosis of Pulmonary Embolus

SINCE THE INCEPTION and development of perfusion lung scanning by Taplin, the primary indication for its use has been in suspected pulmonary embolus. The advantages of this procedure are that it is safe, noninvasive and sensitive. As with most diagnostic procedures of high sensitivity, the abnormalities lack specificity. The major pitfall in interpreting perfusion defects is that reflex pulmonary arteriolar vasospasm occurs with the slightest drop in alveolar oxygen pressure. There-

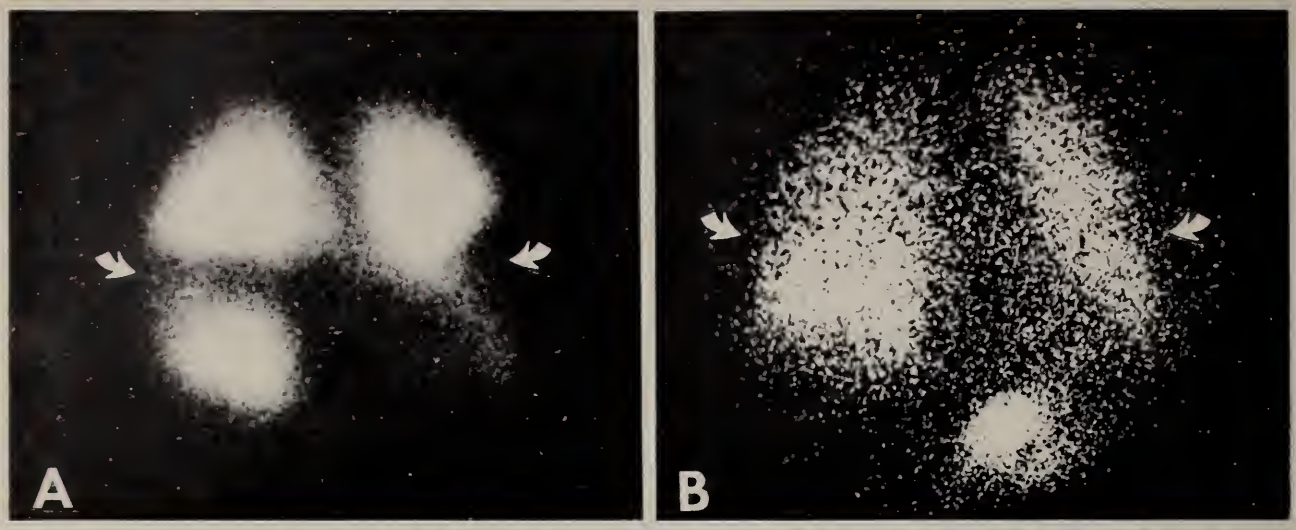


Figure 1.—**A,** anterior view of a perfusion lung scintiphotogram with bilateral perfusion defects indicated by arrows. **B,** inhalation study on the same patient with a radioaerosol showing normal aeration of the nonperfused areas located at arrows. (Activity concentrated at the bottom of image B is swallowed radioaerosol in the stomach.)

fore, it is necessary to evaluate pulmonary ventilation before interpreting perfusion defects.

Each perfusion lung study should include a simultaneous x-ray film of the chest. A radiodensity, whether extraplural (and displacing lung tissue) or parenchymal, should be considered sufficient cause for a perfusion defect.

The differential diagnosis of a pulmonary perfusion defect on lung scan and matching radiodensity on an x-ray film of the chest includes pulmonary embolus with infarction and this entity must remain a clinical and radiographic diagnosis. More commonly, there is no radiographic explanation of the scan abnormality and the differential diagnosis is between pulmonary embolism and localized hypoxia with vasospasm. It is precisely in this instance that the status of that particular airway must be known in order to distinguish primary, that is, pulmonary embolus, from secondary perfusion defects.

There are two scanning techniques for studying the tracheobronchial tree. One makes use of radioxenon with a single breath holding view to detect nonventilated segments followed by a washout study to detect air trapping distal to obstructed airways. Although physiologically ideal, the test has some limitations. Unless it is repeated, only one view is seen. Also, due to the physical properties of the isotope, the xenon study must be obtained before the perfusion scan. An alternative method is to use a radioaerosol which, although nonphysiologic, yields higher resolution images and all four routine views may be obtained. In practice both methods have their place and provide similar information. When comparing the perfusion scan defects with the ventilation study, each abnormality on the perfusion image must be accounted for on the ventilation scan and only mismatches of abnormal perfusion with normal ventilation should be diagnosed as pulmonary embolus (Figure 1).

KENNETH R. LYONS, MD

REFERENCES

McNeil BJ, Holman BL, Adelstein SJ: The scintigraphic definition of pulmonary embolism. JAMA 227:753-756, Feb 1974

Williams O, Lyall J, Vernon M, et al: Ventilation-perfusion lung scanning for pulmonary emboli. Br Med J 1:600-602, Mar 1974

Scintigraphic Diagnosis of Splenic Injuries

BLUNT ABDOMINAL TRAUMA often causes injury to the spleen and, less often, to the liver. Splenic injuries include rupture, laceration and subcapsular hematoma. The latter may lead to delayed rupture days or even weeks later. Therefore, unequivocal evidence of splenic injury is an indication for surgical operation.

Recently published articles on scintigraphy in blunt abdominal trauma, as well as our own experience with more than 1,100 case studies, permit the following conclusions.

- Radiocolloid splenography is very useful in this condition and has an accuracy of approximately 90 percent;
- Its value depends on proper technique, including having multiple oblique and angulated views made under the supervision of a well-

trained specialist, and on its availability for emergency situations.

- It compares favorably with angiography since it is easier to interpret, is noninvasive, is easier to carry out in immobile patients with multiple injuries and takes little time in a well-organized department. Its pictorial detail is adequate for diagnosis in most cases. Angiography can be reserved for the relatively infrequent patient with equivocal findings on a scintigraphic study.
- False negative results of studies are most commonly due to a laceration with free intraperitoneal bleeding. This type of lesion does not create a mass in the spleen but becomes rapidly apparent from the clinical course. False positive studies may be due to preexisting lesions or to misinterpretation of an overlapping left liver lobe by an inexperienced reviewer.
- Concomitant liver images aid in evaluation of possible hepatic involvement.

Consequently, emergency radiocolloid scintigraphy is well suited to serve as the primary special radiologic technique in the workup of patients with suspected trauma of spleen or liver.

JAN K. SIEMSEN, MD
NANCY TELFER, MD

REFERENCES

Rosoff L, Cohen JL, Telfer N, et al: Injuries of the spleen. Surg Clin North Am 52:667-685, Jun 1972

Nebesar RA, Rabinov KR, Potsaid MS: Radionuclide imaging of the spleen in suspected splenic injury. Radiology 110:609-614, Mar 1974

Witek JT, Spencer RP, Pearson HA, et al: Diagnostic spleen scans in occult splenic injury. J Trauma 14:197-199, Mar 1974

Radionuclide Scintigraphy in Cyanotic Heart Disease

QUANTITATION OF right-to-left shunting and determination of the distribution of pulmonary arterial flow can be easily achieved by nuclear medicine techniques. Following intravenous injection of 10 to 50 micron-sized particles of radioactive technetium (^{99m}Tc) macroaggregated albumin (MAA), total body and lung imaging is carried out with a scintillation camera.

The relative distribution of MAA between the lungs is dependent upon partition of pulmonary arterial flow and is determined by the ratios of radioactivity in the lungs. The fraction of MAA which bypasses the lungs to enter the systemic circulation equals right-to-left shunting and is determined as a percentage by: (total body "count" − total lung "count" divided by total body "count") × 100. The albumin per test dose does not exceed 0.2 mg (usual volume is 0.1 ml with a dose of 200 to 400 microcuries) which gives a 6,000-fold safety factor for cerebral toxicity levels.

This procedure provides information useful in the clinical management of cyanotic heart disease. Detection of unilateral pulmonary hyperperfusion by scintigraphy is far more reliable than by usual inspection of chest radiograms where one lung must receive 2 to 2½ times the blood flow of the opposite before consistent detection is possible. Such pulmonary flow imbalance is particularly important to uncover if cardiac surgical procedures are planned or if a systemic-pulmonic anastomosis has been created. Preoperative quantitation of right-to-left shunting will serve as a baseline value for postoperative comparison and allows for objective evaluation of surgical results. Simultaneous determinations of right-to-left shunting and distribution of pulmonary arterial flow has resulted in detection of malfunctioning systemic-pulmonic anastomoses before any other diagnostic procedure. Well-functioning anastomoses reduce right-to-left shunting by increasing pulmonary blood flow to each lung, although sometimes unequally. Malfunctioning anastomoses do not significantly reduce right-to-left shunting and may cause unilateral pulmonary hyperperfusion. Nonfunctioning shunts do not decrease right-to-left shunting but may alter distribution of pulmonary flow. Perfusion lung scans alone are inadequate for evaluating shunt function as preferential nuclide accumulation may occur in either lung regardless of the functional status of the anastomosis.

This technique is carried out in less than 10 minutes, is safe and can be done serially in an outpatient situation. It provides information otherwise obtainable only in part by cardiac catheterization.

GARY F. GATES, MD

REFERENCES

Gates GF, Orme HW, Dore EK, et al: Cardiac shunt assessment in children with macroaggregated albumin Technetium-99m. Radiology 112:649-653, Sep 1974

Gates GF, Orme HW, Dore EK, et al: Surgery of congenital heart disease assessed by radionuclide scintigraphy. J Thorac Cardiovasc Surg 69:767-775, May 1975

Gates GF, Orme HW, Dore EK, et al: The hyperperfused lung in congenital heart disease. JAMA (In Press)

Role of Liver and Bone Scanning in Evaluation of Possible Metastatic Disease

In spite of continuing improvements in equipment and radiopharmaceuticals, the detention efficiency of the liver scan for liver metastasis remains in the 70 to 80 percent range. However, this lack of improvement in accuracy must not be taken as an indication that the scan is not efficacious. A recent National Institutes of Health study again indicates that liver scanning may be more sensitive than the usual clinical or laboratory measurements—serum glutamic oxalic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), bilirubin, alkaline phosphatase—in detecting hepatic metastases.

The evaluation of the bony skeleton has previously been accomplished by the radiologic skeletal survey. However, the bone scan, aided by newer bone-seeking radiodiagnostic agents, has been found to be a more sensitive diagnostic modality. In the face of metastatic disease, results in patients who are given both a bone scan and a skeletal survey will be positive on the scan and normal on x-ray studies. Conversely, abnormal findings on skeletal survey with normal results on bone scan are rare. Abundant recent literature supports the conclusion that the bone scan is the diagnostic method of choice for skeletal evaluation. The bone scan is particularly useful in carcinoma of the lung, breast and prostate, as well as in lymphomas.

Though the bone scan is highly sensitive, its lack of specificity must be noted. To avoid the problem of false positive readings on bone scans, a single x-ray film of the area shown to be abnormal on bone scan should be obtained to exclude nonneoplastic causes of increased osteoblastic activity such as trauma and metabolic, inflammatory or degenerative abnormalities. Initial use of the bone scan for skeletal evaluation will avoid diagnostic overkill, reduce the cost of having both a complete skeletal survey and bone scan and still ensure the highest degree of diagnostic accuracy available in the pretreatment evaluation of neoplastic disease.

Theron Brown, MD

REFERENCES

Levenson SM, Ingle JN, Richman SD, et al: Liver scanning in metastatic carcinoma of the breast. J Nucl Med 16:545-546, Jun 1975 (Abstract)

Bisson J, Vickers M, Fagan WT: Bone scan—In clinical perspective. J Urol 111:665-672, May 1974

ADVISORY PANEL TO THE SECTION ON NUCLEAR MEDICINE

Paul B. Hoffer, MD, *Section Editor, San Francisco*

John R. White, MD
CMA Section on Nuclear Medicine
Chairman
Torrance

Richard C. Ripple, MD
CMA Section on Nuclear Medicine
Secretary
Sacramento

Kenneth Lyons, MD
University of California, Irvine
California College of Medicine

L. Robert Bennett, MD
University of California, Los Angeles

Jorge Franco, MD
CMA Section on Nuclear Medicine
Assistant Secretary
San Jose

William L. Ashburn, MD
University of California, San Diego

Carl Jansen, MD
Loma Linda University

Joseph P. Kriss, MD
Stanford University

Gerald DeNardo, MD
University of California, Davis

William Blahd, MD
CMA Scientific Board
West Los Angeles

Paul B. Hoffer, MD
University of California, San Francisco

Jan Siemsen, MD
University of Southern California
Los Angeles

Robert Kraft, MD
Burlingame

Nancy Telfer, MD
Los Angeles

EDITORIALS

Rational Drug Therapy in Patients with Renal Disease

WILLIAM BENNETT'S PAPER in this issue of the JOURNAL is a welcome and scholarly review of the important topic of drug therapy for patients with renal failure. It will be a difficult article for many physicians to read simply because few clinicians have a working knowledge of the pharmacokinetic formulae presented and consequently may become bogged down by the equations. This is unfortunate because the concepts presented, as well as the principles discussed, should help us to practice better therapeutics. The physician who has difficulty with the article should refer to an explanatory background discussion of these concepts, presented without mathematical detail, that appeared in the *British Medical Bulletin* (27:142-147, 1971).[1]*

The value of understanding the role of the kidney in the pharmacokinetics of drugs stems from its practical importance. Briefly and simply, the role of the kidney in drug kinetics parallels its normal physiologic activities; namely, drug excretion is influenced by filtration, passive transport and active transport. Reduction in filtration for the most part relates directly to reduced drug excretion, if no compensatory mechanisms exist (such as increased hepatic metabolism).[2] The decreased excretion of digoxin and the aminoglycoside antibiotics in azotemia are probably the best known examples of diminished filtration.[3,4] Passive reabsorption is largely dependent on passive, nonionic diffusion; a substance more readily passes through a lipid membrane if it is not ionized, rather than ionized. This phenomenon is clinically important for drugs that are weak acids or weak bases.[5,6] The enhanced excretion of weak acids, such as salicylates and phenobarbital when the urine is alkaline, and diminished excretion of weak bases, such as quinine, amphetamine and ephedrine, underscore the clinical importance of this concept.[7-9] Bennett states that drugs that are most susceptible to this phenomenon have pKa (the pH at which the drug is in equilibrium between the ionized and nonionized state) values in the range of 5.0 to 8.0, but reabsorption of drugs of lower or higher pKa may be affected by small changes in urinary pH. The active tubular transport of drugs is exemplified by the use of probenecid to compete for active renal tubular secretion of penicillin, thereby prolonging its effects. Other drugs, including phenylbutazone, sulfinpyrazone, indomethacin and salicylates, compete for these same pathways and may have clinically important effects on each other's excretion.[10]

For many drugs, the clinical significance of changes in renal function to their administration is unknown. For others, theoretic considerations predict importance, but the appropriate clinical studies have not been published. The importance of *clinical* studies for verification or repudiation of the theoretic expectation must be emphasized. The various formulae provided for calculation of dose or dose interval in patients with renal failure may not be sufficient for all patients. Observed levels of drug may differ from those predicted by a formula or nomogram. Even sophisticated computer programs for estimation of digoxin dosage perform better when given an individual patient's serum level of drug.[11] Further, these formulae do not consider the possibility that, in uremia, alterations in drug metabolism may occur. The importance of clinical studies is also relevant to dialysis in poisoned patients. The decision to dialyze is not based solely on the amount of drug that can be removed, but rather on whether or not clinical studies show that the patient has a better prognosis with dialysis than with conservative management.

Whether to give a patient with azotemia a constant dose of antibiotics at larger dosing intervals, or a reduced dose at constant dosing intervals, is currently being debated. Advocates of the latter approach point out that levels of drug in the serum fluctuate less with small doses at conventional intervals.[1] If a relatively constant level promotes efficacy and diminishes toxicity, this method is clearly preferable. A study comparing these alternatives with gentamicin has shown the

This work was supported in part by NIH grants GM-16496, GM-01791 and HL-06285.

*As a service to our readers and by special arrangement with the *British Medical Bulletin*, the JOURNAL will furnish a reprint of this article upon request. A stamped, self-addressed envelope must be included with your request. Also, the entire issue of the *British Medical Bulletin* in which the article appeared is available for $6.50 (including postage) from 65 Davies Street, London, W 1 Y, 2AA, England.

reduced dose-constant interval method is superior in extremely ill azotemic patients.[12] The results of this study cannot be extrapolated to all antibiotics, but do point out the value of appropriately designed patient studies.

The lack of clinical studies, the limited availability of determinations of serum levels of drugs and the multiple theoretical ways in which drug kinetics could be altered in renal failure may leave a practicing physician unsure of what to do in an individual patient. His primary recourse must and should always be clinical endpoints. The possibility of abnormal kinetics should alert clinicians to signs and symptoms that may indicate either toxicity or lack of efficacy. He can follow serum minimum inhibitory concentrations of an antibiotic one hour after a dose and just before the next; he can look at frequent electrocardiographic rhythm strips of a patient who is taking digoxin; and he can check electrocardiograms of a patient who is taking procainamide (and thus determine lack of efficacy or signs of toxicity). The important points are that the clinician must be aware of the potential for abnormal kinetics in renal failure, he must know the pharmacology of the drugs he selects and he must follow clinical endpoints for drug toxicity and efficacy in each patient.

D. Craig Brater, MD
Howard F. Morrelli, MD
Division of Clinical Pharmacology
Departments of Medicine and Pharmacology
The Cardiovascular Research Institute
University of California, San Francisco

REFERENCES

1. O'Grady F: Antibiotics in renal failure. Br Med Bull 27:142-147, May 1971
2. Weinstein L, Kaplan K: The cephalosporins—Microbiological, chemical, and pharmacologic properties and use in chemotherapy. Ann Intern Med 72:729-739, 1970
3. Jusko WJ, Szefler SJ, Goldfarb AL: Pharmacokinetic design of digoxin dosage regimens in relation to renal function. J Clin Pharmacol 14:525-535, 1974
4. McHenry MC, Gavan TL, Gifford RW, et al: Gentamicin dosages for renal insufficiency—Adjustments based on endogenous creatinine clearance and serum creatinine concentration. Ann Intern Med 74:182-197, 1971
5. Milne MD, Scribner RH, Crawford MA: Non-ionic diffusion and the excretion of weak acids and bases. Am J Med 24:709-729, 1958
6. Prescott LF: Mechanisms of renal excretion of drugs. Br J Anesthesia 44:246-251, 1972
7. Beckett AH, Rowland M: Urinary excretion kinetics of amphetamines in man. J Pharm Pharmacol 17:628-639, 1965
8. Haag HB, Larson PH, Schwartz JJ: The effect of urinary pH on the elimination of quinine. J Pharmacol Exp Ther 79: 136-138, 1943
9. Wilkinson GR, Beckett AH: Absorption, metabolism, and excretion of the ephedrines in man—I. The influence of urinary pH and urine volume output. J Pharmacol Exp Ther 162:139-147, 1968
10. Kampmann J, Hansen JM, Siersbaek-Nielsen K, Laursen H: Effect of some drugs on penicillin half-life in blood. Clin Pharmacol Ther 13:516-519, 1972
11. Sheiner LB, Halkin H, Peck C, et al: Improved computer-assisted digoxin therapy—A method using feedback of measured serum digoxin concentrations. Ann Intern Med 82:619-627, 1975
12. Chan RA, Benner EJ, Hoeprich PD: Gentamicin therapy in renal therapy: A nomogram for dosage. Ann Intern Med 76:773-778, 1972

Malpractice Insurance — Can the Private Sector Do It?

When all the trappings of the malpractice issue are stripped away a very basic question emerges. Can the private sector provide adequate professional liability insurance to practicing physicians at a reasonable cost? This question points directly to the issue of private versus government medicine with all that this implies for all concerned. If the answer is yes, there is an urgent need to find a way to do it, and soon. If the answer is no, there appear to be two principal alternatives. Physicians can treat patients without adequate insurance and risk their own financial security and that of their families if there is a successful suit. Or, if government assumes some responsibility for a physician's professional liability insurance, government may be expected to exercise some surveillance over his practice. Neither of these alternatives is attractive, nor are they likely to be in the best interests of physicians, or their patients.

Can the private sector do it? At the moment the picture is that of the private sector insurance industry in headlong retreat if not in rout from the field of professional liability insurance for physicians. And already some physicians are unable to get insurance or are unable to pay the premiums. Some of these have begun to practice without insurance, others are retiring from practice prematurely, many are limiting their practice to secure lower rates, and others are not entering private practice at all. All of this means that the private, that is nongovernmental, practice of medicine is in serious trouble—as is the care of unknown hundreds or thousands of patients.

In many ways the present situation seems comparable to one that occurred some 40 years ago. At that time there was a severe economic depression and how to finance medical care itself became a critical issue. There were great pressures for government medicine. Then, the private sector seemed unable or unwilling to cope.

Physicians found themselves adrift and embattled with no good means to defend themselves, let alone to develop a workable and lasting solution to the problem. At that time practicing physicians decided to create a means or an instrument with which they could maneuver in the field of financing of patient care. They assumed the responsibility to make this instrument work and they supported it with their energy and substance. History records that Blue Shield has served the profession well through the years in many a difficult situation, and in spite of its ups and downs, Blue Shield continues to be supported by a still growing physician membership, now more than 18,000 in California alone.

Now, much as was the case 40 years ago, the malpractice issue has placed practicing physicians, particularly in California but elsewhere as well, in a situation where the private sector seems either unable or unwilling to cope with an insurance problem, and both physicians and their care of patients are profoundly affected. Again there are great pressures for some kind of governmental intervention, and again physicians find themselves with no adequate means or instrument with which to defend themselves or to develop a workable or lasting solution to what is primarily a social and economic problem in patient care.

Can the private sector do it? At the moment the answer appears to be in doubt, and it would seem that if the answer is to be in the affirmative, the initiative will have to come from somewhere within the health care industry. It is obvious that practicing physicians have the most at stake personally, both for themselves and their patients. If there is anything to be learned from history it would seem the time has now come for the profession to develop an instrument of its own in the field of professional liability insurance, one with which it can not only defend practicing physicians but set standards of quality and efficiency which others in the field will have to meet, and be prepared to support it with both energy and substance.

Time is running out. We cannot wait for the rest of the private sector to act, if indeed it ever will without leadership from private medicine. It is to be hoped that practicing physicians will soon find a way to assume the necessary leadership to do what needs to be done now. The alternatives are clear enough and they are right on our doorstep.

—MSMW

Routine Screening of Asymptomatic Women for Gonorrhea

ELSEWHERE IN THIS ISSUE of the JOURNAL appears a provocative paper by Dr. King K. Holmes on screening methods for detection of asymptomatic gonorrhea. Also in this issue is a sign, designed for display in an examining room, which states that most women who have gonorrhea do not know it and urges patients to "ask for a test."

Although Dr. Holmes disputes the frequency of asymptomatic gonorrhea in the female population, others have estimated that 80 to 90 percent of all women with gonorrhea have no symptoms sufficiently severe to alert them to the need for medical care, and hence do not seek examination and treatment. The United States Public Health Service (USPHS) is now funding a large scale program based on the premise that screening and treating asymptomatic women must become routine practice before the current epidemic of gonorrhea can be contained. The results of this nationwide, federal program are those presented in Table 1 of Holmes' paper.

During the calendar year 1974, more than 900,000 cases of gonorrhea were reported in the United States, but we know that countless others went unreported. Table 1 in Holmes' paper shows the USPHS statistics on the results of cultures from women screened for gonorrhea among various populations throughout the country. Of more than 2¼ million women tested in private physicians' offices, 1.9 percent were noted to have positive cultures. This is an impressive yield for any screening test, and, for example, far surpasses the yield from the Papanicolaou smear which is by now an accepted and standard procedure. Although untreated gonorrhea in women is not lethal, as cervical carcinoma may be, the morbidity in terms of pain, infertility and other complications can be severe. In addition, the spread of gonorrhea must be checked for reasons

of public health as well. The aim therefore is to urge those in the private sector of medicine to screen women routinely for asymptomatic gonorrhea.

The techniques used are of utmost importance. Cervical *smears* for gonorrhea screening in women are a waste of time because of poor sensitivity. Bacterial *culture* from a properly secured cervical specimen is the technique of choice. A rectal specimen taken at the same time further enhances the likelihood of identifying asymptomatic carriers.

There are various means of handling these specimens. In general, a modified Thayer-Martin culture plate incubated in a carbon dioxide enriched atmosphere at 35°C is required. One can use standard Petri dishes or smaller modifications. The culture can be sent to an outside laboratory or it can be incubated in a physician's office. Efficient and relatively inexpensive incubators are now available for such use in an office. The plates can be inspected by an office assistant at 48 hours and then tested with a very quick oxidase reagent procedure if colonies of appropriate morphology are noted. Further testing of the oxidase positive material with Gram stain can be done in a physician's office or in an outside laboratory. Sugar fermentation tests can be done to identify the organism more precisely. Another method is to place the specimen immediately in transport media which allows the otherwise relatively labile Neisseria gonorrhea bacteria to be sent to private or health department laboratories during early stages of incubation.

Some physicians would choose to treat a woman purely on the basis of the oxidase positive culture grown on the selective Thayer-Martin medium; some consider it more appropriate to wait for the results of the Gram stain, and some would insist that treatment wait until a diagnosis is made from the full spectrum of laboratory procedures. Under some circumstances, one may wish to repeat a culture that gave positive findings and send it to a clinical laboratory. One's choice in this matter would depend upon social and economic factors as well as upon scientific considerations.

Plates can be purchased and the screening culture test done for less than $1.00 per patient. The added cost of further testing that the physician might choose to do would apply to a very small proportion of the total population being screened. Government funds are available in some communities through local health departments to provide laboratory support for private physicians or clinics. Many local health departments also have trained staff members available to assist with instructions to physicians and their staffs in proper culture techniques.

We make the plea that each physician develop some fairly broad criteria for screening asymptomatic women for gonorrhea by bacterial culture so that this will become common practice.

David D. Sachs, MD
Chairman
California Medical Association
Task Force on Venereal Disease
San Francisco

Is Obesity a Surgical Disease?

The spectrum of illness which confronts us ranges from immediately life-threatening diseases which require bold intervention to cosmetic ailments which trouble primarily the psyche. Massive, often morbid obesity is at neither extreme of this spectrum, and yet it is an illness with potentially lethal complications. Scientists and insurance companies have addressed themselves to the question of where to draw the line between obesity as a disease and inconsequential fatness. We, as physicians, must wrestle with the issue of what posture we should take toward operations which have been devised to combat obesity. Are these operations currently therapeutic or investigational?

The factors and observations which support the operative treatment of obesity have been clearly delineated in recent years.[1,2] Therefore, either to list the positive features of the results from operations as reported by others, or to repeat the statistics of our personal experience, which has been recently reported in some detail[3] would be redundant. It has become abundantly clear that massively obese people who become lean as a result of jejunoileal bypass are usually highly satisfied. Their self-esteem is so enhanced that they gen-

erally become more positive and more productive members of our society than they were before operation. They are frequently so appreciative of the surgeon's successful efforts that they can be counted almost as disciples. When adverse aftereffects require that normal intestinal continuity be restored, the recommendation is usually accepted only with reluctance and patients almost invariably seek an alternative short of returning to their status before jejunoileal bypass. Thus, the positive features of the results are compelling and they should not be underemphasized.

Detracting from the appeal of operations against fatness are the surgical risks and the undesirable delayed sequellae. The latter range in seriousness from annoyance to death, and the nature of the problems which have been encountered is by now generally known.[1-3] Less well known is the degree to which data reported from various centers are comparable, and impossible to quantitate is the depth of follow-up which each report truly represents.

Personal experience leads us to believe that the nature and incidence of the sequellae to jejunoileal bypass are not fully appreciated. For example, our own data can be variably interpreted depending upon whether we chose to report the greater than 90 percent success rate as measured in terms of weight loss and patient satisfaction, or the 43 percent success rate as measured by our more demanding perception as physicians seeking perfection with a large bank of research data available for study. At most recent compilation, more than half of our patients had some sequel to operation (albeit minor in most instances) which would probably not have occurred without operation. Furthermore, we have been consulted more often for complications which have occurred in patients operated upon elsewhere than for complications suffered by our own patients. For instance, three of our patients who needed repeat operation (two shortenings of the bypass and one takedown) had them done elsewhere, and none of the bypasses we have taken down were created by us. Thus, with less compulsive follow-up than is available to us, and reliance upon clinical impression, we could have erroneously concluded that our patients have been immune from problems requiring reoperation. It is abundantly clear that strict and persistent close follow-up for every patient is imperative to truly understanding the nature and the incidence of the sequellae to jejunoileal bypass. It is equally apparent that this type of follow-up is beyond the scope of that which is usual and practical in the office of busy physicians.

Obesity is a surgical disease. We can no longer view fatness in our patients simply as an annoyance which enhances the difficulty of time-tested operations and predisposes to complications. The courage and originality of those who pioneered in devising operations against obesity commands respect. Yet, neither the availability of operations which are successful in causing weight loss, nor the fact that there are plenty of patients who seek them justifies the widespread use of such operations. We should accept obesity as a surgical disease while jealously guarding the perogative to advise against operation. We should condone operations against obesity only under the proper circumstances, and have the fortitude to stand against their being done whenever the circumstances are not appropriate.

The line between therapy and investigation is not always precise. We began 3½ years ago to accept patients for jejunoileal bypass who are part of a carefully conceived series of interdisciplinary research studies, and we have rejected patients who sought operations purely as therapy. Technical operative pitfalls have been minimized and virtually eliminated. Our operative mortality rate of 3 percent and our additional 3 percent mortality from liver dysfunction are reasonable, and our patients are satisfied. However, a previously unreported delayed complication (colonic pseudoobstruction) has emerged in recent months,[3,4] and we cannot be certain what the future holds even for those of our jejunoileal bypass patients who are currently doing splendidly by all available criteria. Therefore, widespread therapeutic use of jejunoileal bypass against obesity should await better accuracy of prediction than that which is currently possible.

We would suggest that operations against obesity be limited to hospitals prepared to render truly comprehensive care. Recognition of reality precludes recommending that these operations be restricted to clinical study center (CSC) settings, albeit that this remains our conviction. However, the reality that thousands of bypasses have been done outside of CSC settings, neither implies that all operations done without CSC-type of backing were ill-advised, nor does it relieve us of the responsibility to view operations against obesity as investigational at this time. Rather than seek unrealistically and unsuccessfully to stem a tide

which is underway, let us channel it into a useful and constructive stream. Let us recognize the merits of weight reducing operations, but insist that they be permitted only where there is a permanently allied team of physicians and surgeons skilled in the management of obesity and committed to long-term interdisciplinary follow-up which culminates in periodic reporting of results through established professional channels. Let us recognize that anecdotal reporting, either pro or con, is usually misleading, and insist that those willing to take on the operative management of obesity also accept the responsibility for critical indepth analysis of data to be shared with professional peers at a regional or national level. Last, but not least, let us work towards uniformity in criteria for patient selection, and evaluation of results so that today's dilemmas regarding operations against obesity can be expeditiously resolved by summation of comparable data from various centers.

JOHN R. BENFIELD, MD
GEORGE A. BRAY, MD
Departments of Surgery and Medicine
Harbor General Hospital, Torrance
University of California, Los Angeles
School of Medicine

REFERENCES

1. Buchwald H, Varco RL, Moore RB, et al: Intestinal bypass procedures—Partial ileal bypass for obesity. Curr Prob Surg:1-51, Apr 1975

2. Scott HW Jr, Dean R, Shull HG, et al: New considerations in use of jejunoileal bypass in patients with morbid obesity. Ann Surg 177:723-735, 1973

3. Bray GA, Passaro E, Castelnuovo-Tedesco P, et al: Intestinal bypass operation as a treatment for obesity. Ann Intern Med (in press) 1975

4. Fikri E, Cassella PR: Jejunoileal bypass for massive obesity —Results and complications in 52 patients. Ann Surg 179:460-464, 1974

Valuable Clinical Tests for Allergy

THE BRONCHIAL CHALLENGE TEST

. . . The greatest value of a bronchial challenge is when trying to determine which of a group of positive skin tests has clinical significance. And I think bronchial challenge perhaps might be valuable, if any of you have the same problems I have, in dealing with patients who are reluctant to eliminate an animal from their home. I think it would probably be pretty dramatic to have the family in the room and blow a little cat antigen or dog antigen into the child and see the development of asthma. I think even the firmest animal lover would be able to accept this.

—R. G. SLAVIN, MD, *St. Louis*
Extracted from *Audio-Digest Otorhinolaryngology,* Vol 7, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

CASE REPORTS

Refer to: Miller RR, Lewis JP, Knapp W: Acute eosinophilic leukemia associated with neutropenia. West J Med 123: 399-404, Nov 1975

Acute Eosinophilic Leukemia Associated with Neutropenia

RICHARD R. MILLER, MD
JERRY P. LEWIS, MD
WILLIAM KNAPP, MD
Davis and Sacramento

SINCE THE FIRST CASE of eosinophilic leukemia described by Stillman in 1912,[1] case reports[2-5] and reviews of the literature[6,7] have portrayed a high leukocyte count (with a preponderance of eosinophils) and a refractory anemia with associated thrombocytopenia as being features present in a typical patient with this disease. The disease being exceedingly resistant to standard leukemia chemotherapy, the patient's course is one of rapid deterioration.

Our patient differs in several respects from these earlier reports in that the overt leukemic phase was preceded by a very long period of neutropenia and the leukemic phase was associated with persistent leukopenia. Only one other reported case has been noted to lack granulocytosis and none has had prolonged neutropenia documented before the development of overt leukemia. When the patient was admitted to our hospital, there was a high percentage of blasts in the marrow, most of which contained vacuoles. These vacuoles were found in circulating eosinophilic myelocytes as well as in eosinophilic precursors of the bone marrow. Although initially these bizarre cells disappeared with therapy, terminally they returned to the bone marrow and peripheral blood. Finally, whereas most patients with eosinophilic leukemia respond poorly, if at all, to therapy, this patient entered a prolonged remission following treatment with orally given hydroxyurea.

From the Section of Hematology and Oncology, Department of Internal Medicine, University of California, Davis, School of Medicine, and the Department of Internal Medicine, Sacramento Medical Center (Drs. Miller and Lewis); and the Department of Pathology, University of California, Davis, School of Medicine, and Sacramento Medical Center (Dr. Knapp).

Submitted March 11, 1975.

Reprint requests to: J. P. Lewis, MD, Section of Hematology and Oncology, Department of Internal Medicine, TB 155, University of California, Davis, School of Medicine, Davis, CA 95616.

Report of a Case

The patient, a 66-year-old white woman, was referred to the Sacramento Medical Center in July of 1969 by her family physician who had repeatedly documented the patient as having a low peripheral leukocyte count. The patient's symptoms in July were limited to easy fatigability and generalized weakness; these symptoms had been present intermittently for one year. During the late 1920's she was employed as an X-ray technician and for 3½ years had taken an average of 30 films per week. Generally she wore a rubber apron, but was not otherwise shielded from roentgenographic equipment.

In 1953 the patient was noted to be leukopenic, and in 1958 was extensively evaluated for a leukopenia of 2,850 per cu mm. Findings on a peripheral blood leukocyte differential study at that time showed 39 percent of the cells to belong to the neutrophilic cell series. A bone marrow specimen in 1958 was interpreted as being hypocellular. There was no history of drug ingestion or toxic exposure to explain the leukopenia.

In 1968 the patient noted mild dyspnea on exertion, with slight ankle swelling. Mild congestive failure was felt to exist and digitalis was prescribed with resolution of the dyspnea. In that same year the spleen was noted to be barely palpable and laboratory data showed a hemoglobin of 9.7 grams per 100 ml, leukocyte count of 1,000 per cu mm with a differential of neutrophils 9 percent, lymphocytes 64 percent, monocytes 22 percent, eosinophils 4 percent and plasma cells

1 percent. The reticulocyte count was 0.4 percent and the platelet count was 266,000 per cu mm. A bone marrow specimen was reported as being hypercellular with orderly granulocytic maturation and a normal erythroid series. Megakaryocytes were present and were mostly mature. Scattered throughout the marrow were increased numbers of mononuclear cells which were alkaline phosphatase and peroxidase negative. Many of these cells had one or more nucleoli. The marrow interpreter commented that "the presence of immature monocytic and/or histiocytic cells in considerable numbers would indicate that this patient sooner or later should develop a leukemia of the monocytic and/or histiocytic series." We have reviewed these marrow studies and agree that the marrow is disturbing and demonstrates pronounced hypercellularity and monocytosis.

In 1969, when we first saw the patient, the spleen was palpable 4 cm below the left costal margin and the liver was slightly enlarged. Hemoglobin was 9.4 grams per 100 ml with hematocrit of 27.5 percent. Mean corpuscular volume (MCV) was 86 cubic microns and mean corpuscular-hemoglobin concentration (MCHC) 34 percent. A reticulocyte count was 2.2 percent and serum iron was 56 micrograms (μg) per 100 ml with a total iron binding capacity of 228 μg per 100 ml. The leukocyte count was 10,800 per cu mm. This was the only time that the peripheral leukocyte count was documented to be greater than 5,000 per cu mm. The differential on this occasion was banded cells 9 percent, polymorphonuclear cells 4 percent, lymphocytes 24 percent, eosinophils 58 percent, myelocytes 1 percent, promyelocytes 1 percent and myeloblasts 3 percent. Many of the eosinophils were immature and large and contained vacuoles. The myeloblasts and promyelocytes also were vacuolated.

A bone marrow aspiration was carried out without difficulty. The marrow was exceedingly hyperplastic (Table 1, July 1969). Megakaryocytes were notably decreased. Erythropoiesis was hyperplastic with normoblastic maturation and the granulocytic series was notably hyperplastic with a preponderance of blasts, promyelocytes and eosinophilic myelocytes. These cells contained numerous cytoplasmic vacuoles. Many of the eosinophilic granules were large; their color varied from red to orange to gray, with a minority of the granules staining deeply basophilic. The fact that the myeloblasts and promyelocytes were

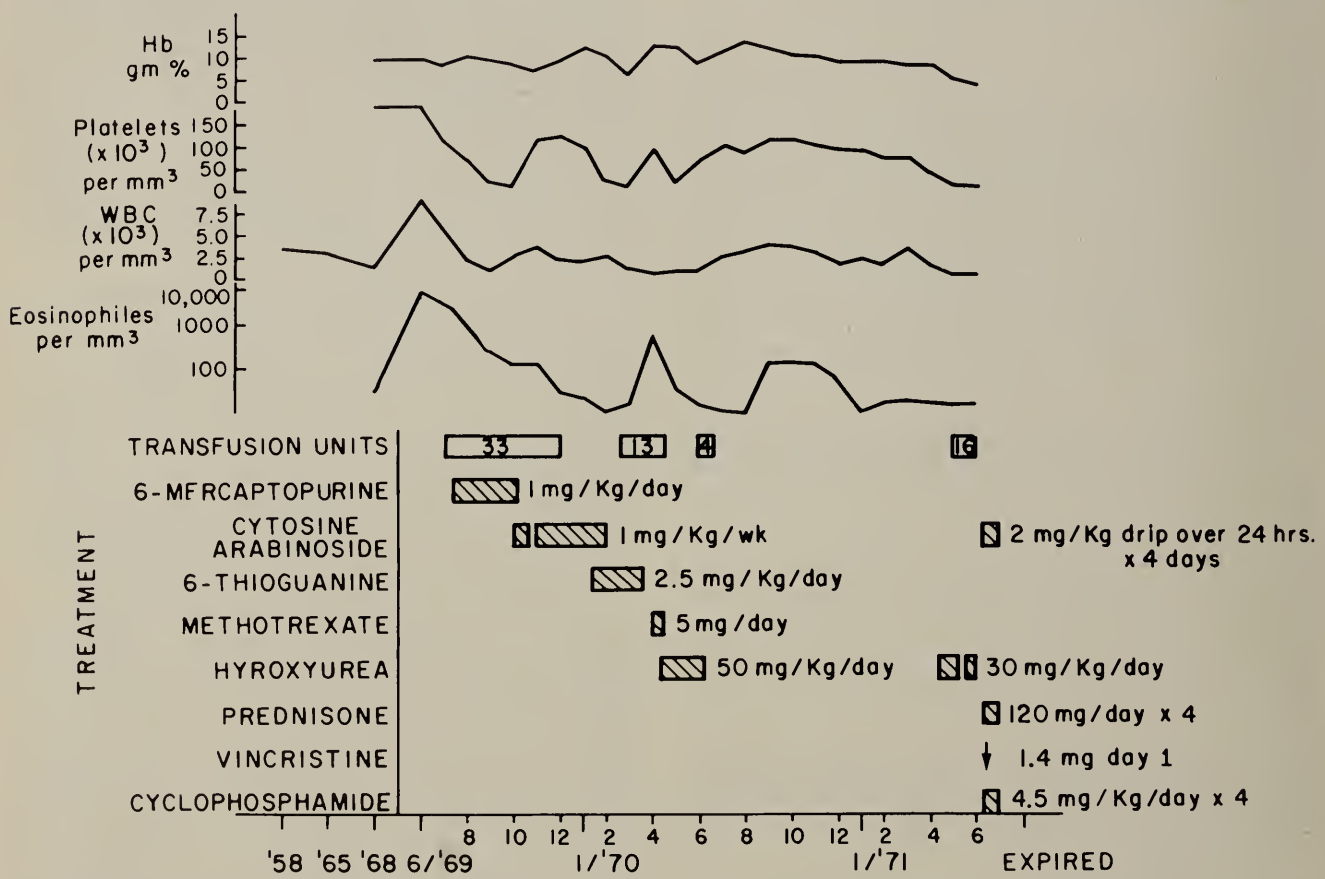


Figure 1.—Summary of peripheral blood data and courses of treatment. (Hb is hemoglobin and WBC is white blood cells, leukocytes.)

vacuolated permitted us to link these cells with the vacuolated eosinophilic myelocytes in the marrow and blood. Some promyelocytes contained a few eosinophilic granules. Similar vacuoles in eosinophilic leukemia have been reported by others.[2]

A diagnosis of eosinophilic leukemia was made and administration of 6-mercaptopurine (1 mg per kg of body weight per day), plus allopurinol, was started. The splenomegaly disappeared, the leukocyte count fell and within three months the bizarre eosinophils had disappeared from marrow and blood.

The patient's clinical course is depicted in Figure 1 and selected marrow differentials are shown in Table 1.

In an attempt to effect a complete remission, various drugs were tried between October 1969 and April 1970. Although the vacuolated myeloblasts and promyelocytes and eosinophilic myelocytes did not return, erythropoiesis was never sufficient to support the patient's hemoglobin needs. It was during this period that findings on a marrow biopsy study first showed evidence of early myelofibrosis. Red cell survivals showed a ^{51}Cr half-life ($t\frac{1}{2}$) of 26 days and ferrokinetic studies showed a plasma $t\frac{1}{2}$ of ^{59}Fe of 120 minutes with no evidence of extramedullary erythropoiesis in liver or spleen. Only minimal erythropoiesis was noted over the marrow. Maximal red blood cell incorporation of ^{59}Fe was only 42 percent by day 13. In early 1970 faint reticular densities of an ill-defined nature were seen on an X-ray study of the chest. These cleared after a few months; however, they reoccurred before death.

TABLE 1.—*Selected Bone Marrow Differentials*

	July 1969	*June 1970*	*May 1971*
Granulocytes			
Neutrophils			
Segmented	2	11	7
Banded	1	7	2
Metamyelocytes	..	18	3
Myelocytes	..	47	1
Promyelocytes	..	7	..
Myeloblasts	..	2	7
Eosinophils			
Segmented			
3 or more lobes	9	..	1
2 lobes	7	..	1
Banded	5	..	..
Metamyelocytes	8	..	6
Myelocytes	23	..	16
Promyelocytes (vacuolated)	13	..	23
Myeloblasts (vacuolated)	26	..	12
Lymphocytes	2	6	15
Plasma cells	..	..	2
Monocytes	2	2	..
Reticuloendothelial cells	2	..	4
TOTAL	100	100	100
Erythroid cells per 100 leukocytes			
Orthochromic normoblast	15	12	8
Polychromatophilic normoblast	13	25	19
Basophilic normoblast	6	24	4
Pronormoblast	1	3	..
Megakaryocytes	Dec'd*	Adq†	Dec'd*
Marrow cellularity (percent of marrow piece with cells)	100	75	60

*Decreased †Adequate

In the latter part of April 1970 administration of hydroxyurea (1 gram per day) was begun. After six weeks the marrow showed dramatic improvement with adequate megakaryocytopoiesis and erythropoiesis. Hemoglobin returned to normal, platelet counts stabilized between 100,000 and 150,000 per cu mm and transfusion requirements ceased. The patient's total peripheral blood granulocyte count was 500 per cu mm, with a total leukocyte count of 3,000 per cu mm. Aside from these two abnormalities in the peripheral blood, which were comparable to those existing for several years before overt leukemia developed, the patient was in a complete remission.

The patient continued without antileukemic therapy from July of 1970 to late April of 1971. During this time she was free of symptoms. In April, however, hemoglobin once again fell, the patient became severely thrombocytopenic and the spleen enlarged. Immature granulocytes with vacuoles and eosinophilic granules again appeared in the peripheral blood. Administration of hydroxyurea was reinstituted without benefit. A four-day course of cyclophosphamide, vincristine, cytosine arabinoside and prednisone induced severe bone marrow aplasia and the patient died with overwhelming Pseudomonas aeruginosa septicemia. The last peripheral leukocyte count recorded was 200 per cu mm with a differential of banded cells 0 percent, polymorphonuclear cells 8 percent, lymphocytes 4 percent, monocytes 56 percent, bizarre eosinophils 4 percent and blasts 28 percent. Many of these blasts contained vacuoles and some had eosinophilic granules.

Postmortem Findings

On postmortem examination, jaundice was noted as well as a deeply eroding left-sided parietal occipital scalp ulcer from which Pseudomonas aeruginosa was cultured. Examination of

the heart showed no endocardial or myocardial fibrosis and there was no evidence of vasculitis. Pulmonary interstitial fibrosis was identified, involving all lobes of the lung. Additionally, focal pulmonary parenchyma osseous metaplasia was noted, bony islands containing viable osteocytes in lacunae with prominent cement lines. An example of the osseous metaplasia is shown in Figure 2. The liver and spleen were enlarged and congested with blood and the lymph nodes were boggy and edematous. Unequivocal leukemic infiltration of lungs, liver, spleen and lymph nodes was not shown. Pleomorphic cells with enlarged irregular nuclei were found infiltrating the bases of acutely penetrating duodenal and jejunal ulcers. Hypocellular sternal and vertebral marrow were populated by scattered atypical cells with enlarged nuclei and occasionally prominent nucleoli; occasional lymphocytes and plasma cells were also seen. The atypical cells within the marrow and in the small bowel were compatible with residual leukemic infiltrates.

Discussion

Eosinophilic leukemia is considered by some to be a variant of disseminated eosinophilic collagen disease,[8,9] a neoplastic response to an immunopathological reaction[10] or a continuum of diseases categorized as hypereosinophilic syndromes,[11] the latter including Loffler's syndrome and endocarditis. Others have considered this disease to be a true malignancy related to chronic granulocytic leukemia,[3,4] while other authors have suggested that eosinophilic leukemia is a distinct malignant myeloproliferative disorder of the eosinophilic cell series.[5,6] We subscribe to the latter interpretation and believe our case contributes to a further understanding of eosinophilic leukemia.

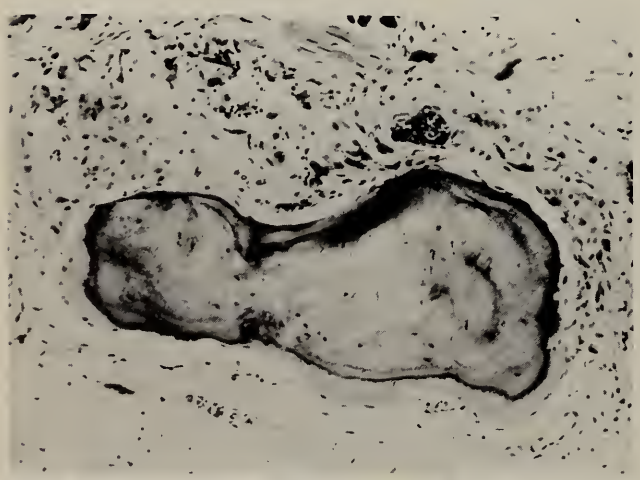


Figure 2.—Low-power view of one of the foci of intraparenchymal pulmonary ossifications identified at autopsy.

Bentley and associates in their excellent review of the subject developed specific diagnostic criteria for eosinophilic leukemia.[6] These were "a marked eosinophilia in the peripheral blood with blast cells above normal in the bone marrow and/or peripheral blood during the course of the illness." They divide previously reported cases of eosinophilic leukemia which meet their criteria into two groups: (1) eosinophilic leukemia beginning with increased blast cells in the peripheral blood or bone marrow or both and (2) mature cell eosinophilic leukemia with an acute or chronic course. Our patient fits best into the acute leukemia classification since she presented with increased blasts in the bone marrow and had an associated peripheral eosinophilia with a predominance of immature forms.

Throughout the course of our patient's illness, a number of the more commonly found manifestations of eosinophilic leukemia were noted.

When initially seen at the Sacramento Medical Center, the patient had hepatosplenomegaly. This resolved while under therapy but recurred before death.

Before the patient was seen at the medical center, mild congestive heart failure had developed which was never adequately explained. Congestive heart failure has been related directly to cardiac pathology of endocardial fibrosis and occasionally eosinophilic infiltration. Development of fibrosis has been thought to be related to release of eosinophilic granules containing lysozymes which then induce a myocardial fibrotic reaction. This is most commonly seen in patients in whom there are pronounced elevations in peripheral blood eosinophils.[6,7] Autopsy data on our patient suggest that earlier cardiac findings were probably not related to leukemia, however.

In 16 percent of patients with eosinophilic leukemia, pulmonary lesions are seen sometime during the course of illness, and at autopsy pulmonary pathology is found in 40 percent. During life, lung roentgenographic abnormalities generally consist of transient pulmonary reticular densities. These have been related to thickening of alveolar walls and patchy consolidation due to eosinophilic cell infiltrates in the lung parenchyma. Again, it has been postulated that release of acid phosphatases, lysozomes and peroxidase enzymes in the lung from the eosinophilic cells might result

in pulmonary pathology.[7,12] In our patient, there were pulmonary reticular densities in 1970 and terminally extensive pulmonary infiltrates were noted At autopsy the lungs showed pulmonary fibrosis and distributed widely throughout the lung parenchyma were foci of intraparenchymal pulmonary ossifications. The bone formation was not found in association with bronchi or bronchioles and appeared to be highly differentiated with good cement lines and Haversian systems. The osteocytes were viable. The significance of this unique finding is not known; however, it has been reported in conjunction with administration of antileukemic chemotherapeutic agents. The pulmonary fibrosis has been assumed to be a forerunner of the intrapulmonary ossification,[13-15] and pulmonary fibrosis has been associated with eosinophilic leukemia[6,7] and was a prominent finding late in this patient's course. The fact that in our patient notably elevated peripheral blood eosinophils were not present throughout the entire course of the disease may have explained why pulmonary involvement in this case was minimal until the terminal phase of disease. The low eosinophil count may explain also why no cardiac pathology was found.

Several features of disease in our patient were atypical of eosinophilic leukemia yet are not uncommonly seen in other forms of adult acute leukemia. Of particular interest was the rather prolonged period of neutropenia which, as least for part of the time, was associated with a hypercellular marrow. This type of preleukemic state is found typically in patients presenting with myelomonocytic leukemia but has not been reported previously in patients with eosinophilic leukemia.[16] The marrow study made in 1968 had many features typical of patients with the preleukemic syndrome. What relationship, if any, this premalignant phase of her disease had to the X-ray exposure is unknown. It is likely that although the patient was exposed to radiation in 1930, this did not increase substantially the possibility of leukemia developing. From experience with atomic bomb survivors, it is thought the peak incidence of postradiation leukemia is 8 and 13 years.[17] Of course, sufficient time has not elapsed to permit observations on the effect of such radiation 35 to 40 years later.

Throughout the patient's leukemic phase, with the exception of a single peripheral leukocyte count one month before therapy, the total peripheral leukocyte count was below 5,000 per cu mm. This has not been reported before in eosinophilic leukemia. In fact, in only one case in the literature has the patient presented with a normal peripheral leukocyte count.[18] Therefore, the neutropenia of this case is most unusual.

The response to chemotherapy in our patient was also of interest, and atypical of eosinophilic leukemia. In 1969 the patient presented with a slightly elevated leukocyte count and a high percentage of eosinophils. We began administration of 6-mercaptopurine, to which the response was clearing of immature eosinophils from the peripheral blood and bone marrow. Anemia and thrombocytopenia persisted, however. After trying several chemotherapeutic agents, administration of hydroxyurea was begun. A prompt favorable response ensued with normalization of hemoglobin and platelet count. During a nine-month period of quiescence in the patient's disease no therapy was required and the abnormal eosinophils did not return; however, two months before the patient's death vacuolated blasts once again were identified in marrow (Table 1, May 1971). Some of the promyelocytes and myelocytes contained the typical eosinophilic granules seen in the eosinophilic cell line at the time the initial diagnoss of acute eosinophilic leukemia was made. Terminally, the patient's marrow had been rendered nearly aplastic by vigorous chemotherapeutic measures. There were, however, residual scattered primitive cells in bone marrow and in bases of small bowel ulcers compatible with leukemic cells.

This case extends the clinical picture of eosinophilic leukemia to encompass clinical features associated with some cases of adult acute leukemia, including a so-called preleukemic phase and a neutropenic blood picture during active leukemia. The rather impressive response to hydroxyurea in this case suggests this form of therapy might be useful in other cases of this very aggressive form of acute leukemia.

Addendum

Since acceptance of this paper Chusid and Dale have published a case report entitled "Eosinophilic Leukemia: Remission with Vincristine and Hydroxyurea" Am J Med 59:297-300, 1975. These authors report a case of eosinophilic leukemia in which there was a complete remission after administration of prednisone, vincristine and hydroxyurea. The patient was then maintained in

a complete remission for more than a year with administration of hydroxyurea alone. These authors conclude, as did we, that hydroxyurea appears to have a role in the management of eosinophilic leukemia.

REFERENCES

1. Stillman RG: A case of myeloid leukemia with predominance of eosinophile cells. M Rec 81:594-595, 1912
2. Friedman M, Wolman IJ, Tyner HH: Eosinophil leukemia—With report of a case. Amer J Med Sci 208:333-343, 1944
3. Kauer GL Jr, Engle RL Jr: Eosinophilic leukaemia with Ph¹-positive cells. Lancet 2:1340, 1964
4. Gruenwald H, Kiossoglou KA, Mitus WJ, et al: Phildelphia chromosome in eosinophilic leukemia. Am J Med 39:1003-1010, 1965
5. Goh KO, Swisher SN, Rosenberg CA: Cytogenetic studies in eosinophilic leukemia—The relationship of eosinophilic leukemia and chronic myelocytic leukemia. Ann Intern Med 62:80-86, 1965
6. Bentley HP Jr, Reardon AE, Knoedler JP, et al: Eosinophilic leukemia—Report of a case, with review and classification. Am J Med 30:310-322, 1961
7. Benvenisti DS, Ultmann JE: Eosinophilic leukemia—Report of five cases and review of literature. Ann Intern Med 71:731-745, 1969
8. Odeberg B: Eosinophilic leukemia and disseminated eosinophilic collagen disease—A disease entity? Acta Med Scand 177:129-144, 1965
9. Pierce LE, Hosseinian AH, Constantine AB: Disseminated eosinophilic collagen disease. Blood 29:540-549, 1967
10. Bengtsson E: Eosinophilic leukemia—An immunopathological reaction? Acta Paediat Scand 57:245-249, 1968
11. Resnick M, Myerson RM: Hypereosinophilic syndrome—Report of two cases, with prolonged courses. Am J Med 51:560-564, 1971
12. Vaughn J: The function of the eosinophile leukocyte. Blood 8:1-15, 1953
13. Ewing J: Neoplastic Diseases, A Treatise on Tumors, 4th Ed. Philadelphia, W. B. Saunders Company, 1940, p 221
14. Oliner H, Schwartz R, Rubio F Jr, et al: Interstitial pulmonary fibrosis following busulfan therapy. Am J Med 31:134-139, 1961
15. Leake E, Smith WG, Woodliff HJ: Diffuse interstitial pulmonary fibrosis after busulphan therapy. Lancet 2:432-434, 1963
16. Saarni MI, Linman JW: Myelomonocytic leukemia—Disorderly proliferation of all marrow cells. Cancer 27:1221-1230, 1971
17. Anderson RE: Leukemia and related disorders. Human Path 2:505-514, 1971
18. Hule VV: Die akuten basophilen und eosinophilen Leukosen. Sang 21:423-436, 1950

Refer to: Bayer AS, Brenner RJ, Galpin JE, et al: Severe disabling polyarthritis associated with bacterial endocarditis. West J Med 123:404-406, Nov 1975

Severe Disabling Polyarthritis Associated with Bacterial Endocarditis

ARNOLD S. BAYER, MD
R. JAMES BRENNER, MD
JEFFREY E. GALPIN, MD
LUCIEN B. GUZE, MD
Torrance, California

THE DIAGNOSIS of infective endocarditis is often elusive, and atypical presentations may mislead the physician into considering other diseases.[1] We have recently seen a young woman wth endocarditis whose chief presentation was severe, disabling, bilaterally symmetrical polyarthritis. We report this unusual case with a brief review of the literature concerning the joint manifestations of infective endocarditis.

From the Department of Medicine, Harbor General Hospital, Torrance; the Department of Medicine, University of California, Los Angeles, School of Medicine, and the Research and Medical Services, Wadsworth Hospital, Veterans Administration Center, Los Angeles.

Submitted March 4, 1975.

Reprint requests to: A. S. Bayer, MD, Division of Infectious Disease, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

Report of a Case

A 22-year-old woman was admitted to Harbor General Hospital in August 1974 because of severe joint pains. She had been in good health until ten days before admission, when she noted the gradual onset of intense pain, stiffness and pronounced swelling in both ankles. In the seven days before admission, similar symptoms developed in both knees, wrists and shoulders. About this time a nonpruritic rash developed on both feet. The joint pains and swelling were of such magnitude that the patient became totally bedridden for the week before admission. Chills and fever had been present during the ten days before admission to hospital. There was no history of syphilis or gonorrhea, and her last sexual contact had been four weeks before admission.

The patient indicated that there had been no abuse of drugs (either orally or intravenously). She was taking no medications and noted allergy to penicillin. There was no history of rheumatic fever. There were no recent dental, genitourinary or gynecological manipulations.

On physical examination, the patient's vital signs were temperature, 39.5°C (103.1°F); pulse, 100 per minute; respiratory rate, 16 per minute,

and blood pressure, 110/70 mm of mercury. There were no Roth's spots, petechial hemorrhages or clubbing. There was a nontender erythematous rash on the dorsum of both feet. The chest was clear to percussion and auscultation. There was no neck vein distension. On cardiac examination, a grade II/VI, soft, nonradiating systolic ejection murmur was noted at the lower left sternal border. There were no gallops or rubs. There was no hepatosplenomegaly or lymphadenopathy. On joint examination warmth and extensive swelling of the ankles, knees and shoulders was seen. There was also tenosynovitis of both wrists. There was extreme pain and pronounced limitation of motion of all involved joints. Results of pelvic and neurologic examinations were within normal limits.

At admission, laboratory values were hematocrit 36 percent, leukocyte count 3,600 per cu mm, with a normal differential, and a platelet count of 250,000 per cu mm. Intermediate purified protein derivative (PPD) and coccidioidin skin tests gave reactive readings. Serum urea nitrogen, creatinine, electrolytes, antistreptolysin O titer and C-reactive protein were within normal limits. Sickle cell preparation was negative. Serum albumin was slightly decreased at 2.8 grams per 100 ml (normal 3.0 to 5.0 grams per 100 ml), and serum gamma globulin was notably elevated at 4.6 grams per 100 ml (normal 0.4 to 1.5 grams per 100 ml). Results of a serum Venereal Disease Research Laboratories (VDRL) test were positive at a 1:2 dilution, and of a fluorescent treponemal antibody absorption test (FTA-ABS) were weakly positive. Studies for serum rheumatoid factor and antinuclear antibody gave negative findings. Serum complement levels were not obtained. Results of repeated urinalyses were within normal limits. Although the knees, ankles and shoulders were notably swollen, only 2 ml of fluid could be aspirated on multiple attempts. The fluid was turbid, yellow in appearance. The viscosity was grossly normal by "string test." No cells were seen on microscopic examination; Gram stain showed no organisms. No crystals were seen under polarized light. Cultures of the fluid on blood agar, eosin-methylene blue (EMB) agar and Thayer-Martin agar (under 5 percent carbon dioxide) were negative. Insufficient joint fluid prevented quantitation of glucose and protein content. Cultures of the rectum, pharynx and cervix on Thayer-Martin agar (under 5 percent carbon dioxide) yielded no organisms. Findings on electrocardiogram were within normal limits. No abnormalities were seen on an x-ray film of the chest or on films of all the involved joints.

Intravenous administration of erythromycin was begun, 1 gram every six hours, because of the suspicion of disseminated gonococcemia. There was no improvement in symptomatology over the next 48 hours. On echocardiography, normal excursion of the anterior leaflet of the mitral valve was noted; however, the tracing was interpreted as consistent with a left atrial myxoma. A right heart catheterization was done, but failed to show a myxoma.

Four sets of blood cultures, drawn on admission, were subsequently reported as positive for Group D enterococci (according to the criteria of R. R. Facklam[2]). Administration was started of vancomycin hydrochloride, 500 mg every six hours given intravenously, and streptomycin sulfate, 500 mg every 12 hours given intramuscularly. On the fourth day of therapy, skin testing for penicillin hypersensitivity was done. The patient did not react to either the major or minor determinants, and aqueous penicillin G, 12 million units per day given intravenously, was substituted for the vancomycin. All joint signs and symptoms abated by the fifth day of therapy and repeat blood cultures gave negative results at that point. The infection was cured with a four week course of parenteral penicillin and streptomycin, interrupted by two leaves of absence taken by the patient against medical advice. It is of interest that the enterococcal bacteremia and severe joint symptoms recurred during one of these interruptions. The serum complement (B_1 C) was 150 mg per 100 ml (normal 140 to 164 mg per 100 ml) at the time of clinical and bacteriologic relapse. Blood cultures at the termination of therapy were sterile and the patient has remained well since.

Discussion

Although joint complaints are often associated with bacterial endocarditis,[3] severe symmetrical polyarthralgia and polyarthritis as a presenting syndrome has not been emphasized in the literature. Horder, in 1909, reported joint pains, "indefinite both in situation and cause," in 66 of his 150 patients.[4] He noted modest joint swelling in 27 of these patients, but in a later paper[5] remarked on the decreasing frequency of joint effusions in cases of bacterial endocarditis. Lib-

man is noted as not having seen objective signs in the joints of patients with bacterial endocarditis.[5] Thayer's review noted little more than the presence of joint pains in most of his patients.[7] Kerr in his extensive monograph on endocarditis described the joint findings as arthralgias which were "fleeting" in nature.[6]

Most reviewers since Kerr's publication have also alluded to joint complaints in bacterial endocarditis, but not as the main presenting syndrome and rarely as severe and incapacitating as in the present case.[1,3,8,9] Arthralgias remain fairly common and very occasionally a minor effusion is noted in one or two joints. However, polyarthritis with significant swelling in multiple joints is extremely unusual.[1,3,8-10]

Suppurative arthritis is uncommonly associated with bacterial endocarditis. In two large recent series of patients with purulent arthritis, bacterial endocarditis was not found as the cause in any of the 120 cases recorded.[11,12] In 50 cases of endocarditis cited by Banks and co-workers,[13] just one patient presented with a septic arthritis. Similarly, Tompsett reviewed 76 patients with endocarditis; in only one was suppurative arthritis present.[14] In the latter two instances, the infection was monoarticular.

The many other diseases that might manifest in a similar fashion make a polyarthritic mode of presentation even more difficult to diagnose as infective endocarditis. As was shown in the present case, several other entities that often present with symmetric polyarthritis (such as disseminated gonococcemia, collagen vascular disease and atrial myxoma) were initially considered before bacterial endocarditis was eventually diagnosed.

Still to be elucidated are the possible mechanisms of the joint manifestations of infective endocarditis. Whether they are caused by immune complex deposition[10] or by bland or infectious emboli, remains to be answered. Unfortunately, we were not able to obtain enough joint fluid to do the necessary studies to define the exact mechanisms involved (that is, a search for antigen-antibody complexes, complement studies and nitroblue tetrazolium testing),[15] nor were we able to obtain joint tissue for immunofluorescent studies and electron microscopy. The finding of pronounced joint swelling with but only small quantities of sterile joint fluid obtainable by aspiration, suggests that the pathologic process may have been limited to the synovial lining, a situation not dissimilar from that suggested for the early polyarthritis of gonococcal sepsis, where an immune complex cause has been suspected.[16] Of note was the rapid reversal of the present patient's extensive polyarthritis when standard combination antibiotic therapy for enterococcal endocarditis was instituted.[8,17] Also of interest was the recurrence of the entire clinical syndrome shortly after a suboptimal course of antimicrobial therapy was given,[8] with blood cultures again being positive for Group D enterococci.

Summary

A patient with enterococcal endocarditis presented with severe, progressive, symmetric polyarthritis with sterile joint fluid. Appropriate antimicrobial therapy resulted in cessation of the bacteremia and a rapid resolution of the extensive polyarthritis. Clinicians should be aware of this unusual mode of presentation of infective endocarditis, a disease in which early recognition and proper therapy may be lifesaving.

REFERENCES

1. Weinstein L, Rubin R: Infective endocarditis 1973. Progr Cardiovasc Dis XVI:239-274, Nov/Dec 1973

2. Facklam RR: Comparison of several laboratory media for presumptive identification of enterococci and Group D steptococci. Appl Microbiol 26:138-145, Aug 1973

3. Chase RM: Infective endocarditis today. Med Clin North Am 57:1383-1393, Nov 1973

4. Horder TJ: Infective endocarditis, with an analysis of 150 cases and with special reference to the chronic form of the disease. Q J Med 2:290-324, 1909

5. Horder TJ, Libman E: Discussion on the Clinical Significance and Course of Subacute Bacterial Endocarditis. Proceedings of the Section of Medicine, the 88th Annual Meeting of the British Medical Association. Br Med J 2:301-311, 1920

6. Kerr A: Subacute Bacterial Endocarditis. Springfield, Bannerstone House, 1955, p 153

7. Thayer WS: Studies on bacterial (infective) endocarditis. Johns Hopkins Hospital Report 22:1-185, 1926

8. Lerner PI, Weinstein L: Infective endocarditis in the antibiotic era. N Engl J Med 274:199-206, 259-266, 323-331, 388-393, Jan 27, Feb 3, Feb 10, Feb 17, 1966

9. Finland M, Barnes MW: Changing etiology of bacterial endocarditis in the antibiotic era. Ann Intern Med 72:341-348, Mar 1970

10. Hayward GM: Infectious endocarditis—A changing disease. Br Med J 2:706-709, Jun 23, 1973

11. Argen RJ, Wilson CH, Wood P: Suppurative arthritis—Clinical features of 42 cases. Arch Intern Med 117:661-666, May 1966

12. Kelly PJ, Martin WJ, Coventry MB: Bacterial (suppurative) arthritis in the adult. J Bone Joint Surg 52:1595-1601, Dec 1970

13. Banks T, Fletcher R, Nayab A: Infective endocarditis in heroin addicts. Am J Med 55:444-451, Oct 1973

14. Tompsett R: Bacterial endocarditis—Changes in the clinical spectrum. Arch Intern Med 119:329-332, Apr 1967

15. Gupta RC, Steigerwald JC: Nitroblue tetrazolium test in the diagnosis of pyogenic arthritis. Ann Intern Med 80:723-726, Jun 1974

16. Holmes KK, Counts GW, Beety HN: Disseminated gonococcal infection. Ann Intern Med 74:979-993, Jun 1971

17. Watanakunakorn C, Bakie C: Synergism of vancomycin-gentamicin and vancomycin-streptomycin against enterococci. Antimicrob Agents Chemother 4:120-124, Aug 1973

Refer to: Shettigar UR, Pfeifer JF, Hultgren HN: Demand pacemaker for refractory atrial tachycardia in a patient with aortic regurgitation. West J Med 123:407-411, Nov 1975

Demand Pacemaker for Refractory Atrial Tachycardia in a Patient with Aortic Regurgitation

U. R. SHETTIGAR, MBBS
JAMES F. PFEIFER, MD
HERBERT N. HULTGREN, MD
Palo Alto

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA may precipitate heart failure or angina in patients with organic heart disease. The degree of hemodynamic disturbance may depend on the age of the patient, the extent of underlying heart disease and the rate and duration of tachycardia. Vagal stimulation maneuvers and conventional drug therapy are usually effective in terminating attacks. However, an occasional patient may not respond to these measures. Electrophysiologic studies may be of value in such a patient to define the mechanism of the tachycardia and evaluate alternate methods of therapy.

This report concerns a patient in whom moderate aortic regurgitation was present and who was severely incapacitated by frequent attacks of paroxysmal atrial tachycardia which were refractory to drug therapy. A transvenous demand ventricular pacemaker was implanted which could be converted by the patient to a fixed mode by placing a magnet over the pulse generator during episodes of tachycardia. Retrograde depolarization of the atrium stopped the tachycardia. This method has been successful in terminating multiple episodes of tachycardia over a ten month follow-up period.

From the Cardiology Division, Veterans Administration Hospital, Palo Alto, California.

Submitted March 13, 1975.

Reprint requests to: Herbert N. Hultgren, MD, Veterans Administration Hospital, 3801 Miranda Avenue, Palo Alto, CA 94304.

The use of this method in terminating episodes of tachycardia has been used by Ryan and coworkers in a patient with supraventricular tachycardia associated with Wolff-Parkinson-White (WPW) syndrome,[1] and by Kitchen and Goldreyer in a patient with paroxysmal atrial tachycardia unassociated with WPW syndrome.[2]

Report of a Case

A 56-year-old white man was admitted to Palo Alto Veterans Administration Hospital in July 1973 for evaluation of aortic regurgitation and paroxysmal atrial tachycardia of approximately 30 years duration. In 1942 a heart murmur was first noted during a routine physical examination. The first episode of tachycardia occurred in 1943. Since that time, there have been approximately five episodes of tachycardia each year, usually terminated by Valsalva's maneuvers and occasionally requiring sedatives. In 1958 pulmonary edema developed following a prolonged attack of tachycardia. Oral administration of digoxin was started in 1966. Quinidine sulphate was added in 1971 because more frequent attacks of paroxysmal atrial tachycardia were occurring.

In 1972 the patient was admitted to hospital twice for the management of persistent tachycardia associated with dyspnea and weakness (Figure 1). He was forced to quit his job as a jeweller because of frequent, disabling attacks of tachycardia. In 1973 the patient was taken to the emergency room of a local hospital on several occasions for the treatment of recurrent episodes of tachycardia associated with dyspnea, fatigue and dizziness. Conversion to sinus rhythm was achieved with drug therapy which included digoxin, quinidine and propranolol.

The patient has been sedentary in recent years and there has been no exertional dyspnea, nocturnal dyspnea, orthopnea, syncope or chest pain.

The history and family history were unremarkable. There was no background of smoking or excessive consumption of alcohol.

On physical examination in July 1973 the blood pressure was 150/70 and the heart rate was 78 per minute and regular. The carotid pulse was

ABBREVIATIONS USED IN TEXT

APD = atrial premature depolarizations
cps = cycles per second
WPW = Wolff-Parkinson-White (syndrome)

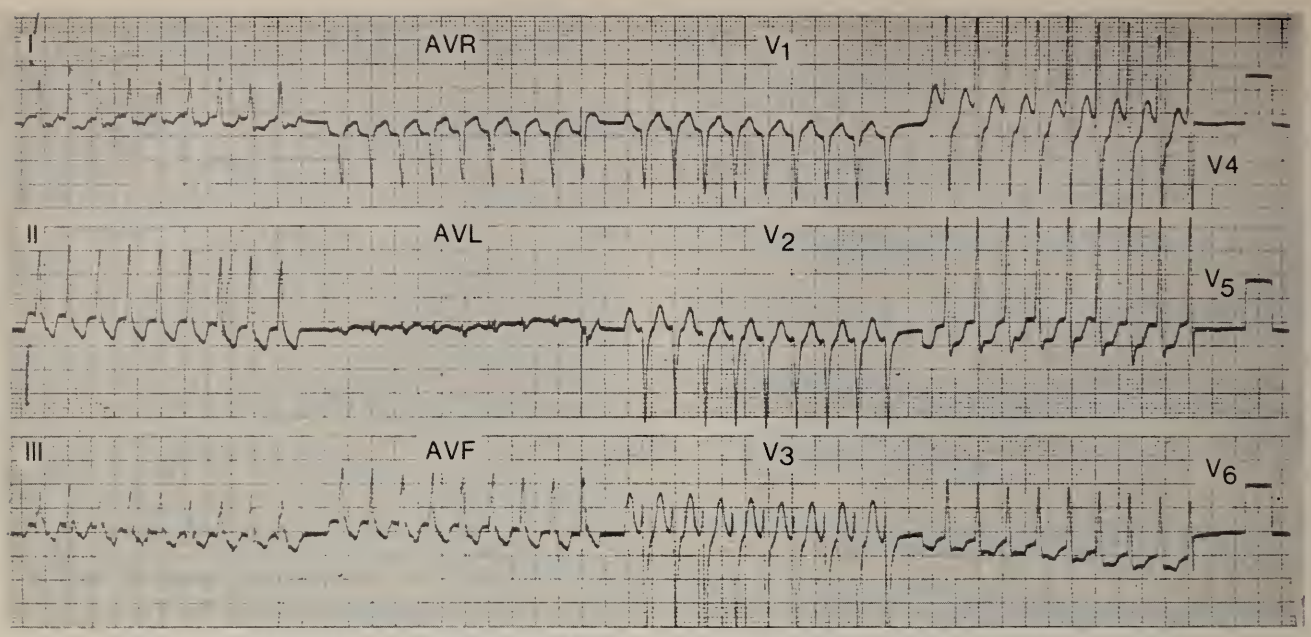


Figure 1.—Electrocardiogram showing supraventricular tachycardia at a rate of 240 per minute

bounding with a rapid upstroke. There were no abnormal precordial impulses. On auscultation there was a grade 2/6 ejection systolic murmur heard best over the right upper sternum and a grade 3/6 diastolic blowing murmur was present along the left sternal border. Findings on laboratory studies were within normal limits except for Type IV lipoproteinemia. On electrocardiogram left ventricular hypertrophy by voltage criteria was noted (Figure 2) and there was no indication of ventricular preexcitation in any of the records. Mild left ventricular enlargement was seen on cardiac roentgenograms but there was no evidence of heart failure.

Cardiac catheterization (July 16, 1973) revealed normal resting pressures. The left ventricular end-diastolic pressure was 20 mm during moderate supine exercise. On an aortic root angiogram a moderate degree of aortic regurgitation was noted associated with a noncalcified tricuspid aortic valve.

Following discharge from the hospital, more frequent and persistent attacks of atrial tachycardia occurred associated with left ventricular failure and hypotension, which were refractory to the usual drug therapy and required repeated cardioversions. The patient was admitted to hospital in September 1973 and again in October 1973 and during this time cardioversion was carried out 12 times while digoxin, quinidine and propranolol were administered, with blood levels of these drugs in the therapeutic range.

On October 18, 1973 a right atrial and ventricular pacing study was done in conjunction with recording of His's bundle and atrial electrograms.

Method and Results

Using mild sedation and local anesthesia a quadripolar electrode catheter was introduced through the right medial basilic vein and positioned against the lateral wall of the right atrium in such a way that the terminal electrodes were in contact with the lower right atrial wall and the proximal electrodes were in the vicinity of the sinoatrial (SA) node. The terminal electrodes were used for recording the atrial electrogram and the proximal electrodes were used for pacing the right atrium. Another identical quadripolar electrode catheter was inserted percutaneously via the right femoral vein and positioned such that the terminal electrodes were in contact with the apex of right ventricle and were subsequently used for pacing the right ventricle. The proximal electrodes were positioned just under the tricuspid valve and were used for recording the His's bundle electrogram. Externally, the recording leads of both electrode catheters were connected through an electrode switch box (Model BMS-4, E for M) into the Electronics for Medicine multi-channel recorder. Bipolar His's bundle electrograms were recorded with the frequency response limits of the amplifier set to a low of 40 cycles per second (cps) and a high of 500 cps. A lead II surface electrocardiogram was also recorded. Medtronic external pacemaker (Model No. 5880) was used for pac-

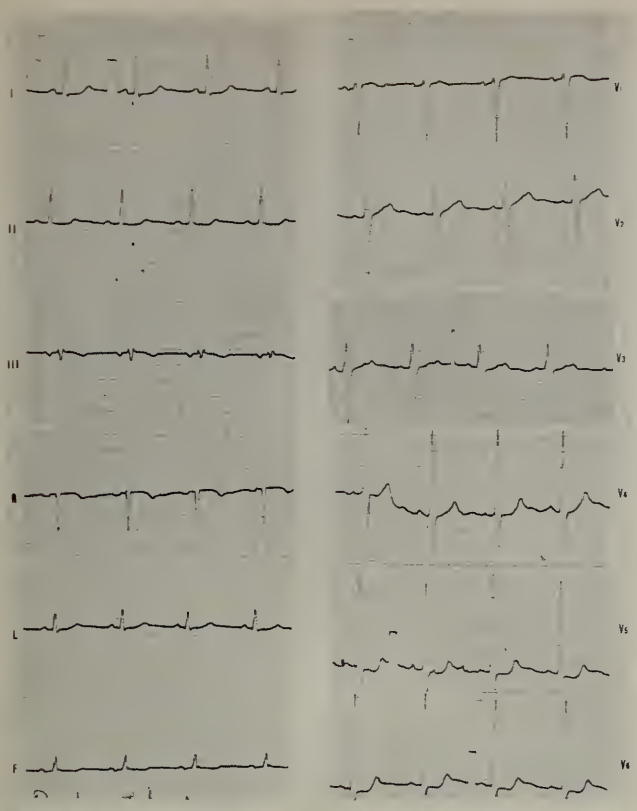


Figure 2.—Electrocardiogram shows normal sinus rhythm and evidence of left ventricular hypertrophy.

ing the atrium. The patient was in sinus rhythm during the study. It was possible to elicit atrial premature beats by delivering the atrial stimuli at random. Atrial tachycardia was repeatedly induced when atrial premature depolarizations (APD) were elicited during a critical period of cardiac cycle [between 200 and 250 milliseconds after the QRS onset (Figure 3)]. It was noted that these atrial premature depolarizations were conducted to the ventricle with a prolonged arterioventricular (AV) conduction time (prolonged PR interval), presumably due to their arrival at the AV node during its relative refractory period. As observed by others previously[3,4] such a prolonged AV conduction time is necessary for the atrial reentry to occur. Atrial tachycardia thus induced was easily converted to sinus rhythm by pacing the atrium or the ventricle (Figure 4) at a fixed rate. Conversion to sinus rhythm occurred in a matter of a few seconds when pacing rate was over 120 per minute but it took longer (one to five minutes) when the pacing rate was 70 per minute.

A-H and H-V intervals were within normal limits at rest and during tachycardia. There was no indication of ventricular preexcitation or WPW syndrome.

Following the pacing study a temporary transvenous fixed rate pacemaker (rate, 70 per minute) catheter was left in the right ventricle and the patient was sent to the coronary care unit under observation.

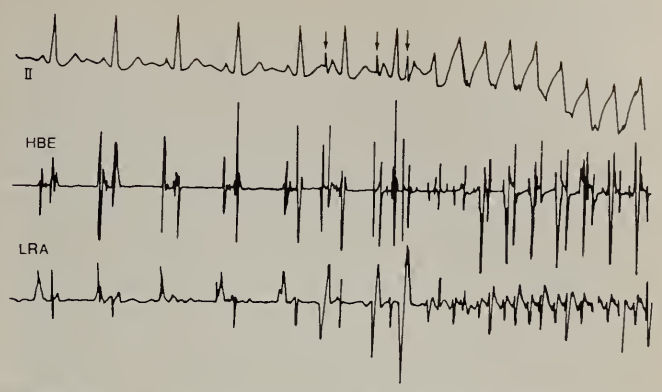


Figure 3.—The initiation of atrial tachycardia by paced atrial stimuli (as indicated by arrows) is shown. Note atrial tachycardia at a rate of 160 per minute with aberrant ventricular conduction. His's bundle electrogram (HBE) and low right atrial electrogram (LRA) have been retraced. II indicates lead II electrocardiogram.

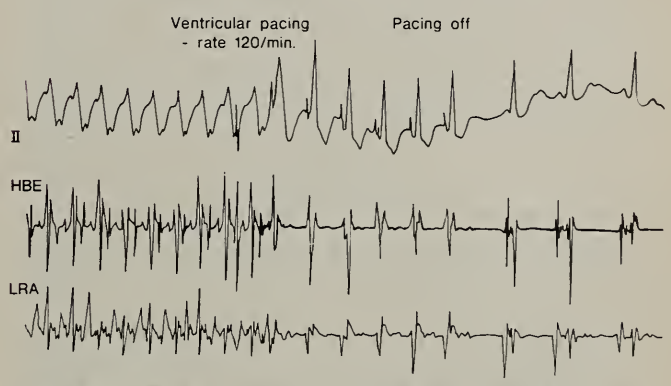


Figure 4.—The conversion of atrial tachycardia by ventricular pacing is shown. Note the resumption of sinus rhythm after the pacemaker was turned off. His's bundle electrogram (HBE) and low right atrial electrogram (LRA) records have been retraced. II indicates standard lead II electrocardiogram.

On several occasions the patient was able to terminate spontaneous attacks of atrial tachycardia within a few minutes by briefly switching on the pacemaker.

Subsequently, a permanent Medtronic (Model No. 5943) transvenous demand pacemaker set at a rate of 68 per minute was implanted and the patient was instructed to apply an external magnet over the pulse generator if tachycardia should develop. During the ten months following implantation of the permanent pacemaker, the patient has successfully terminated paroxysmal tachycardia on 40 occasions. He has remained virtually asymptomatic and is again able to work as a jeweller.

Discussion

Paroxysmal atrial tachycardia is frequently seen in normal population groups and usually is of no hemodynamic consequence. Often it subsides spontaneously without any treatment. When paroxysmal atrial tachycardia occurs in the presence of organic heart disease it may follow a strikingly different course. In this patient, atrial tachycardia occurred in the presence of moderately severe aortic regurgitation and ultimately resulted in the development of severe left ventricular failure when episodes of tachycardia persisted. The atrial rate during tachycardia in this patient varied between 160 and 240 per minute. This is an uncommon finding which may be due to either more than one reentrant pathway involved in sustaining the atrial tachycardia or to variable rates of conduction in the reentrant pathway. Occasionally, atrial tachycardia in this patient was associated with aberrant ventricular conduction. A WPW syndrome was never shown even during a His's bundle study when aberrant ventricular conduction was easily shown.

Disability appeared related to both the rate and duration of tachycardia. Following failure of drug therapy to control paroxysmal atrial tachycardia, replacement of aortic valve was considered but was abandoned in view of the fact that the degree of aortic insufficiency was not severe. Other invasive procedures were then considered primarily for the management of paroxysmal atrial tachycardia.

The use of an electronic carotid sinus nerve stimulator[5] was considered but since vagal stimulating maneuvers and parasympathomimetic drugs had already failed, it was abandoned. Surgical resection of AV node with implantation of permanent ventricular pacemaker has been reported in cases of refractory paroxysmal atrial tachycardia associated with the WPW syndrome.[6] This is a major surgical procedure and the outcome is not always certain.[3,7] If the patient required aortic valve replacement for severe aortic regurgitation, this procedure may have been given more consideration.

Another approach to the problem is the use of a demand or synchronous permanent pacemaker with the pacing electrodes positioned in the right atrium, coronary sinus or right ventricle. At the onset of tachycardia, the patient can convert the demand function of the pacemaker into fixed (asynchronous) mode by holding a magnet externally over the pulse generator. The magnet inactivates the sensing circuit of the pacemaker when it is applied over the pulse generator converting the demand mode of the pacemaker into a fixed mode. This would result in a competitive rhythm and converison of paroxysmal atrial tachycardia. When the paced impulse occurs during a certain critical period of the cardiac cycle, the reentry pathway is rendered refractory to the oncoming circus wave front. Ryan and co-workers first described the use of a right ventricular demand pacemaker and an external magnet in treating a patient in whom there was refractory paroxysmal atrial tachycardia associated with WPW syndrome.[1] Kitchen and Goldreyer successfully used a similar technic in a patient with paroxysmal atrial tachycardia but this time with no evidence of ventricular preexcitation.[2] Preston and associates treated a patient in whom WPW syndrome was present associated with paroxysmal tachycardia with implantation of a permanent left atrial pacemaker.[8] The pacemaker was turned off at all times except during the episodes of tachycardia. The patient activated it by placing a magnet over the pulse generator. Atrial pacing at a rate of 108 per minute always terminated the tachycardia within a minute.

In this patient it was elected to leave the pacing catheter in right ventricle in preference to right atrium since we observed that ventricular paced impulse conducted retrogradely causing atrial depolarization and was effective in converting the atrial tachycardia. Moreover, it is difficult to position a catheter in right atrium such that it would remain stable over a long period of time. Pacing from the coronary sinus was not considered in view of the reports of high rate of pacing failures and complications.[9]

The pacemaker has been effective in quickly terminating the atrial tachycardia on 40 occasions in the ten months of follow-up. On two occasions it took about ten minutes to convert the tachycardia; however, none of these attacks resulted in any symptoms more severe than palpitation. A possible hazard of having a fixed rate pacemaker in the ventricle (during the application of magnet) would be the development of ventricular tachycardia or fibrillation and the risk would increase if the time taken for conversion of tachycardia were prolonged. Normally, however, the fibrillation threshold is noted to be 10 to 30 times greater than the ventricular pacing or stimulation threshold, thereby providing a margin of

safety between the normal pacing threshold and the fibrillation threshold.[10,11] The risk of pacemaker triggered ventricular fibrillation is probably small in the absence of acute myocardial ischemia or severe heart disease, digitalis toxicity and severe electrolyte or acid-base imbalance. Zoll reported no increased incidence of sudden death in their patients treated with asynchronous ventricular pacemakers[12] and Furman and co-workers observed that sudden, unexplained deaths were equally frequent in their patients whether treated by asynchronous (fixed rate) or synchronous (demand) pacemakers.[13] Barold and associates reported the magnetic reed switch of the pulse generator "sticking" in the open position in a patient, making it impossible to revert the pulse generator to its fixed mode of pacing with the application of the magnet.[14] This seems to be an uncommon pacemaker malfunction and perhaps can be corrected in the newer models.

Prolonged conversion time noted in our patient appears to be related to the relatively slow asynchronous pacing rate (68 per minute) of the pacemaker. This problem probably might be remedied by using a radiofrequency-coupled or inductively coupled atrial pacemaker. A recent report by Fruehan and co-workers described the successful use of a competitive radiofrequency-coupled atrial pacemaker in a patient with refractory paroxysmal atrial tachycardia.[15] Williams and co-workers found inductively coupled atrial pacemakers quite effective in terminating paroxysmal supraventricular tachycardia in two patients.[16] One shortcoming is that a thoracotomy is required for implantation of atrial electrodes. However, the results appear to be quite satisfactory.

We conclude that the use of a transvenous ventricular demand pacemaker for the management of refractory paroxysmal atrial tachycardia is a safe and effective procedure, especially in patients who cannot tolerate thoracotomy for the implantation of atrial leads. Long-term follow-up and further experience, however, are needed.

Summary

This report concerns a patient in whom there were a moderate degree of aortic regurgitation and frequent, persistent attacks of atrial tachycardia associated with severe symptoms of heart failure and in whom the conventional drug therapy failed. Electrophysiologic studies showed the mechanism of the tachycardia to be due to atrial reentry or circus movement involving the atrioventricular junction. Pacing from the right atrium as well as the right ventricle was effective in terminating the tachycardia within a few seconds to minutes. A permanent transvenous right ventricular demand pacemaker was implanted. The patient was able to apply an external magnet over the pulse generator at the onset of a bout of paroxysmal tachycardia, thereby converting the demand mode of pacing into a fixed mode and terminating the tachycardia usually within three minutes. This therapeutic measure was effective in controlling frequent episodes of tachycardia in this patient in the ten months of follow-up. The use of a transvenous ventricular demand pacemaker for the management of refractory paroxysmal supraventricular tachycardia is an effective procedure, especially in patients who are refractory to medical treatment.

REFERENCES

1. Ryan GF, Easley RM Jr, Zaroff LI, et al: Paradoxical use of a demand pacemaker in treatment of supraventricular tachycardia due to WPW syndrome—Observation on termination of reciprocal rhythm. Circulation 38:1037-1043, 1968

2. Kitchen JG, Goldreyer BN: Demand pacemaker for refractory paroxysmal supraventricular tachycardia. N Engl J Med 287:596-599, 1972

3. Bigger JT Jr, Goldreyer BN: The mechanisms of supraventricular tachycardia. Circulation 42:673-688, 1970

4. Goldreyer BN, Bigger JT Jr: Site of re-entry in paroxysmal supraventricular tachycardia in man. Circulation 43:15-26, 1971

5. Braunwald E, Sobel BE, Braunwald NS: Treatment of paroxysmal atrial tachycardia by electrical stimulation of the carotid sinus nerves. N Engl J Med 281:885-887, 1969

6. Dreifus LS, Nichols H, Dryden M, et al: Control of recurrent tachycardia of WPW syndrome by surgical ligature of the A.V. bundle. Circulation 38:1030-1036, 1968

7. Cole JS, Wills RE, Witerscheid LC, et al: The WPW syndrome problems in evaluation and surgical therapy. Circulation 42:111-121, 1970

8. Preston TA, Kirsh MM: Permanent pacing of left atrium for treatment of WPW tachycardia. Circulation 42:1073-1077, 1970

9. Siddons H, Sowton E: Cardiac pacemakers. Springfield, Charles C Thomas, 1968, pp 58-172

10. Dressler W, Jonas S, Rubin R: Observations in patients with implanted cardiac pacemaker—IV. Repetitive responses to electrical stimuli. Am J Cardiol 15:391, 1965

11. Zoll PM, Linenthal A: External electric stimulation of heart. Assn NY Acad Sci 167:1055, 1969

12. Zoll PM: Types of pacemakers and their reliability, chap 10, *In* Meltzer LE, Kitchell JR (Eds): Current Concepts of Cardiac Pacing and Cardioversion. Philadelphia, Charles Press Publishers, Inc, 1971, p 193

13. Furman S, Escher DJW, Solomon N: Experience with myocardial and transvenous implanted cardiac pacemakers. Am J Cardiol 23:66, 1969

14. Barold SS, Gaidula JJ, Castillo R: Unusual response of demand pacemakers to magnets. Br Heart J 35:353-358, 1973

15. Fruehan TC, Meyer JA, Klie JH, et al: Refractory paroxysmal supraventricular tachycardia—treatment with patient controlled permanent radio frequent atrial pacemaker. Am Heart J 87:229-237, 1974

16. Williams DO, Davison PH: Long term treatment of refractory supraventricular tachycardia by patient-controlled inductive atrial pacing. Br Heart J 36:336-340, 1974

Refer to: Tri TB, Combs DT: Phenothiazine induced ventricular tachycardia. West J Med 123:412-416, Nov 1975

Phenothiazine Induced Ventricular Tachycardia

TERRY B. TRI, MD
DARREL T. COMBS, MD
San Francisco

VENTRICULAR TACHYCARDIA has been reported as a complication of large doses of phenothiazines.[1-8] It was described first in dogs where massive doses of chlorpromazine (75 to 85 mg per kg of body weight) administered over a period of 1 to 2 hours almost uniformly resulted in this arrhythmia.[1] Subsequently, eight cases have been reported,[2-8] six of which terminated fatally.[4-8] In five of these cases,[2,3,5,7,8] thioridazine was the offending agent; in two others,[5,6] combinations of thioridazine and other phenothiazines; and in one,[4] chlorprothixen was the apparent etiologic agent. In four[4-6] of these eight cases, however, serious systemic illnesses existed which might have induced the ventricular arrhythmia. One was associated with an overdose of chlorprothixen and its attendant hypoxia,[4] one with a severe aspiration pneumonitis and the use of multiple arrhythmogenic agents,[6] one with septic shock[5] and the other with chest pain and pathological changes suggesting a myocardial infarction.[5] The role of the phenothiazines in the last two cases has been questioned by Wendkos.[9] The other four reports[2,3,7,8] describe induction of ventricular tachycardia and document its temporal relationship with phenothiazine therapy in patients who had no history of cardiac disease. Two of these patients survived and had no recurrence of arrhythmia after withdrawal of phenothiazine therapy.[2,3]

From the Cardiology Service, Department of Medicine, Letterman Army Medical Center, San Francisco.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Submitted revised March 5, 1975.

Reprint requests to: Technical Publications Editor, Letterman Army Medical Center, Presidio of San Francisco, CA 94129.

Coronary arteriography was carried out on the patient described by DeSautels and co-workers[3] and no abnormalities were found.

Recently, we treated a patient who had no history or clinical evidence of cardiac disease, and in whom ventricular tachycardia developed after the institution of thioridazine therapy. This represents another well-documented case of phenothiazine induced ventricular arrhythmia and the patient is another survivor of such an episode.

Report of a Case

A 54-year-old woman was admitted February 19, 1973 to the Psychiatric Service, Letterman Army Medical Center, with a diagnosis of manic depressive psychosis. The patient had been in hospital numerous times for recurrent psychiatric problems since 1947. There was no history of allergies; and neither the patient nor her family had a history of cardiovascular disease.

On physical examination, the temperature was 36.9°C (98.4°F), pulse 72 beats per minute, respirations 20 per minute and blood pressure 136/80 mm of mercury. The patient appeared disoriented and rambling speech and flight of ideas were noted. Results of an examination of the chest were within normal limits, except for severe thoracolumbar kyphoscoliosis. There was no cardiomegaly, jugular venous distention or hepatojugular reflux. The first and second heart sounds were normal. A grade 2/6 systolic flow murmur was audible at the left sternal border without radiation. There were no gallops and there was no peripheral edema. On a roentgenogram of the chest, no active cardiopulmonary disease was seen and findings on the initial electrocardiogram were within normal limits.

The patient was treated with 200 mg of thioridazine (Mellaril®) four times daily and 500 mg of thorazine at bedtime. After two weeks of therapy the acute manifestations of psychosis had resolved. Except for an Escherichia coli urinary tract infection, which was treated with cephalexin monohydrate (Kerflex®), the patient was generally well. On the evening of March 4, 1973, sudden cardiopulmonary arrest occurred while the patient was being attended on the latrine. Mouth-to-mouth respiration was begun and a firm blow to the chest was delivered. Spontaneous heart beat and respiration returned within two to three minutes. The patient was transferred to the coronary care unit.

Findings on physical examination and chest

roentgenogram were unchanged from the findings at admission. An electrocardiogram (Figure 1) showed sinus tachycardia, notched broad T waves and prolongation of the Q-T interval to 500 msec ($Q\text{-}T_c = 0.62$ sec). The patient's dose of 200 mg of thioridazine was inadvertently administered and four hours later two episodes of ventricular tachycardia developed which were successfully terminated each time with a 50 mg bolus dose of lidocaine intravenously. The next day there were five more episodes of ventricular tachycardia (Figure 2), despite a continuous lidocaine drip (4 mg per min). These necessitated seven additional lidocaine injections (50 mg bolus each), 250 mg of procainamide (Pronestyl®), every three hours and three direct current cardioversions. The following morning, the Q-T interval had shortened to 380 msec and administration of lidocaine was discontinued without recurrence of the arrhythmia. The procainamide was discontinued four days later. Throughout this period, findings on serial cardiac enzyme (serum glutamic oxaloacetic transaminase [SGOT], lactic dehydrogenase [LDH] and creatine phosphokinase), electrolyte and arterial blood gas studies were within normal limits. Electrocardiograms showed resolution of the notched T waves and normalization of the prolonged Q-T interval. There were never any changes suggestive of a myocardial infarction.

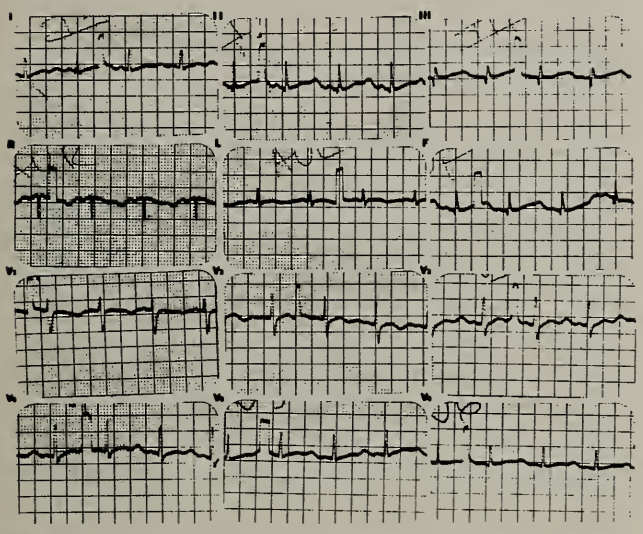


Figure 1.—Electrocardiogram taken at time of transfer to the Cardiology Service. Note the pronounced prolongation of the Q-T interval to 500 msec with characteristic notched T wave.

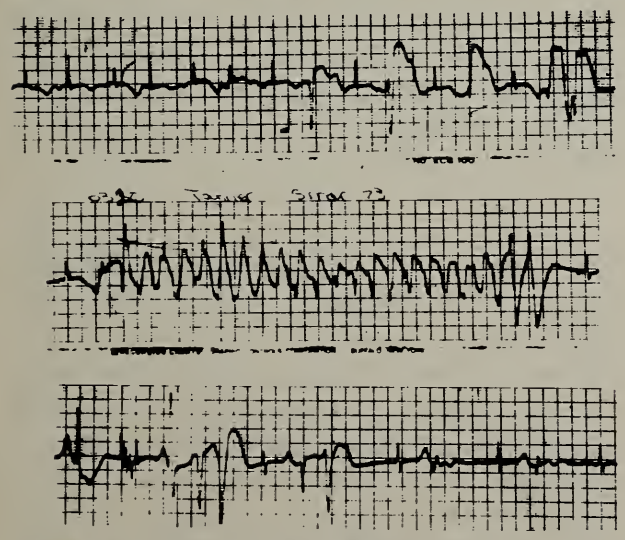


Figure 2.—Rhythm strips obtained during one of the episodes of arrhythmia. Frequent premature ventricular contractions (PVC) lead into a short run of ventricular tachycardia when a PVC occurs during the vulnerable period. This episode terminated spontaneously.

After a 96 hour arrhythmia-free interval, the patient was returned to the psychiatric ward. She remained well without signs of cardiac disease and was discharged on March 13, 1973. Findings on electrocardiograms had returned to normal (Figure 3). Reevaluated by the Cardiology Service in June 1973, the patient was asymptomatic and electrocardiographic findings were normal. She had continued to do well without medication.

Discussion

Electrocardiographic changes have been described in association with phenothiazine therapy.[1,5,10-18] The more frequent abnormalities include blunting, flattening, broadening, notching or inversion of the T wave and prolongation of the Q-T interval. These occur in 50 to 100 percent of patients taking thioridazine,[5,10-16] 50 per-

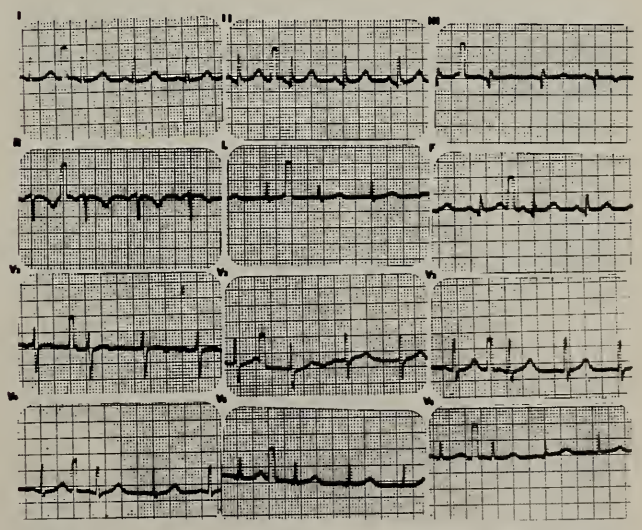


Figure 3.—Electrocardiogram taken shortly before discharge. The Q-T interval is now 360 msec ($Q\text{-}T_c = 0.43$ sec) and there has been normalization of the T wave configuration.

cent of patients on chlorpromazine[10,12] and 16 percent of patients on trifluoperazine.[10] The abnormalities appear to be dose related. In 50 percent of patients treated with thioridazine therapy, repolarization abnormalities develop on doses of 100 to 300 mg per day and on doses greater than 300 mg, abnormalities develop in approximately 75 percent of patients.[12] These electrocardiographic repolarization alterations have been rereversed by fasting in 57 percent of the patients,[18] in 90 percent with propranolol[18] and in 100 percent with potassium salts, nitrates and ergot alkaloids,[13,15,16] or by discontinuing or reducing the dosage of the phenothiazine.[11,14] The mechanism involved in the production of these abnormalities remains unknown and their significance disputed.

Wendkos[15,16] and Huston and Bell[12] feel that these repolarization disturbances are benign and that the reported sudden deaths and rhythm disturbances in patients on phenothiazines do not result from the medication, particularly when the medication is administered in conventional doses. Peele and von Loetzen[19] hypothesize that these deaths are either lethal catatonia or the autopsy-negative sudden, unexpected cardiac death found in the normal population. Others,[6,20,21] however, strongly disagree with this interpretation; they point out that sudden unexplained death in psychotic patients is a new entity, appearing after the introduction of the phenothiazines in 1959. Its occurrence in young people, and the distinct histologic changes found at autopsy, suggest that phenothiazine cardiac toxicity with arrhythmia is the actual cause of death.[13,22,23] Certainly, the present case, as well as the four previously well documented cases[2,3,7,8] of ventricular tachycardia temporally related to phenothiazine therapy in patients without apparent antecedent cardiac disease, incriminates the medication as the etiologic agent of the arrhythmia. The lack of evidence for electrolyte abnormalities, blood gas disturbances and ischemic heart disease; the disappearance of the arrhythmia upon cessation of the drug, and the absence of recurrence of the arrhythmia in those who survived further supports such a concept. However, it must be remembered, as pointed out by Alvarez-Mena and Frank[18] that there is as yet no directly acquired electrophysiologic data to prove a direct cause-and-effect relationship between phenothiazine administration and ventricular arrhythmias.

Some authors[7,12,15] have suggested that phenothiazine induced arrhythmia only occurs in patients given extremely large doses. All but one of the reported cases[2] had received between 1,500 and 3,600 mg of thioridazine, (the manufacturer's recommended dosage is 800 mg per day).[7] However, the patient reported by Schoonmaker and co-workers[2] who received only 600 mg of thioridazine per day and the present case suggest that massive doses are not always required for the induction of an arrhythmia.

The pathogenesis of phenothiazine induced arrhythmias is unknown, but there are at least four general mechanisms postulated: (1) nonhomogeneous phenothiazine electrical suppression, (2) catecholamine imbalance, (3) direct cardiotoxicity and (4) alteration of ion fluxes.

Nonhomogeneous Phenothiazine Electrical Suppression

The first postulated mechanism involves a nonhomogeneous electrical suppressive effect of phenothiazine on the myocardium. These agents have suppressive antiarrhythmic effects on various atrial and ventricular arrhythmias in both animals[24] and man,[25] and the electrocardiographic changes produced are not unlike those of quinidine.[2] Presumably, if the drug suppresses one part of the myocardium more than another, a reentry pathway may result which could then initiate an arrhythmia. Certainly, quinidine induced ventricular tachycardia is a well-known entity.

Catecholamine Imbalance

An imbalance of circulating or myocardial concentration of catecholamines or both is another postulated mechanism for the repolarization abnormalities and arrhythmias. Leestma and Koenig[8] suggest that the phenothiazines may sensitize the myocardium so as to predispose it to epinephrine induced arrhythmias. Others[5,7,14,22] propose that phenothiazines, either through a direct effect on the myocardial cell or through their action on central nervous system autonomic centers, alter the amount or effect of catecholamines on the myocardial cells to a varying extent and the attendant imbalance triggers an arrhythmia. The transient termination of the electrocardiographic repolarization abnormalities by propranolol tends to support such a theory. However, Schoonmaker and co-workers[2] found that propranolol was ineffective in controlling ventricular tachycardia in their patient and interpreted this as evidence that the sympathetic nervous system could not be implicated as its cause.

Direct Cardiotoxicity

A direct toxic effect of phenothiazines on myocardial cells resulting in structural change, impaired function, irritability and resultant arrhythmia is the third postulated pathogenetic mechanism. Greiner and Nicolson[26] found at autopsy widespread pigment deposition in myocardial fibers as well as in the skin and other viscera in bodies of patients who had been treated with phenothiazines and who died suddenly and unexpectedly. Since thioridazine retinal pigmentation resulted in retinal dysfunction it seemed reasonable that the cardiac pigment deposition represented evidence for phenothiazine induced cardiac dysfunction. They considered this to be melanin and attributed its accumulation to a disorder of pigment metabolism provoked by the prolonged administration of phenothiazines. Zelickson[27] subsequently suggested that this was not true melanin, but possibly pseudomelanin, a drug metabolite or other pigment. More recently Hollister and Kosek[6] have shown that the pigment is more likely lipofuscin and its presence is not causally related to phenothiazine.

Richardson and associates[20] found a different cardiac lesion. They did not find widespread pigment deposition, but instead they found collections of mucopolysaccharide material in the smaller arterioles of the subendocardial region with focal or diffuse myocardial malacia.

Some of these lesions were in the specialized conduction tissue which provided an explanation for the arrhythmias. In addition, such small vessel disease can result in focal ischemia or necrosis and thereby produce an irritable focus that might initiate arrhythmias.[22] However, Leestma and Koenig[8] have raised doubt that this histologic appearance is specific. It apparently is found commonly in untreated patients.

Alteration of Ion Fluxes

The last postulate regarding the pathogenesis of these arrhythmias is that phenothiazines alter the distribution of ions across the myocardial cell membrane. This is mediated either through a direct effect on membrane permeability or through an effect on the membrane bound magnesium dependent sodium-potassium adenosine triphosphatase (Na-K ATPase) enzyme system. The net result is a change in membrane potential and a delay in the reestablishment of the full negative potential that makes up the process of repolarization. This explains the prolongation of the Q-T interval. The delayed repolarization results in prolongation of the vulnerable period and the attendant increased electrical nonhomogeneity from temporal dispersion of recovery sets the stage for reentry arrhythmias.[18] There is a considerable amount of evidence to suggest that this may actually be the operant mechanism in phenothiazine arrhythmias.

The Na-K dependent ATPase enzyme system appears to be an integral part of the "sodium pump" which maintains the membrane potential and may play a role in repolarization of a nerve or muscle cell following an action potential.[8] Magnesium is required as an activating factor for this enzyme system. It has been suggested that phenothiazines have some ability to chelate heavy metals, including magnesium, and through this mechanism they poison the "sodium pump."[8] Huston and Bell[12] have shown that urinary excretion of magnesium is increased during oral thioridazine administration to humans; and substituted phenothiazines inhibit Na-K dependent ATPase in rats' brain.[29] However, Huston and Bell[12] also found that myocardium of rats was depleted of sodium after intraperitoneal administration of thioridazine, and Landmark[17] showed that in rats phenothiazines reduced potassium-42 efflux from isolated myocardial cells in the process of prolonging repolarization. These effects are just the reverse of what one would expect if the drug's only effect was the poisoning of the Na-K dependent ATPase "sodium pump." Therefore, although there is preliminary evidence that the pathogenesis of phenothiazine repolarization abnormalities and arrhythmias involves an inhibitory effect on the myocardial cell membrane bound Na-K ATPase enzyme system, this is probably not their only effect. The additional changes in ion fluxes that cannot be explained by this model suggest that there are other operant mechanisms on myocardial cell membrane permeability that have yet to be elucidated.

Comment

The existence of phenothiazine induced ventricular arrhythmia as a clinical entity can no longer be disputed. The frequency of occurrence remains open to question. Certainly, since there are only nine reported cases in the indexed English language literature despite the frequent use of phenothiazines suggests that it is an uncommon manifestation; however, there probably are a con-

siderable number of cases that go unrecognized and unreported.[30] It is also clear that high doses of phenothiazines are not required for the development of this complication. The fact that electrocardiographic changes are common with phenothiazine therapy despite the apparent rarity of ventricular arrhythmia makes it difficult to determine in which patients this potentially fatal complication is likely to develop. The presence of pronounced prolongation of the Q-T interval appears to be the most consistent finding in the cases reported in the literature. This evidence of a significant phenothiazine myocardial effect should serve as a sign of potential life-threatening cardiac toxicity.

This review of the literature would seem to suggest that phenothiazines should only be used in reasonable dosage levels and patients should be monitored periodically by electrocardiography. Until further information is available, it would seem prudent to discontinue the medication or reduce the dosage if significant prolongation of the Q-T interval develops. If ventricular arrhythmia occurs, the patient should be treated with lidocaine,[7] procainamide,[3] direct current cardioversion[2,7] with or without an internal pacemaker.[2]

Summary

Ventricular tachycardia temporally related to thioridazine therapy developed in a 54-year-old woman (without evidence of antecedent heart disease). Typical phenothiazine electrocardiographic changes were present including notched T waves and prolongation of the Q-T interval. These changes and the arrhythmia resolved after thioridazine was discontinued. A search of the literature uncovered eight similar cases.

The possibilities for the mechanism of arrhythmogenesis include nonhomogeneity in myocardial suppression, induction of catecholamine imbalance, direct myocardial toxicity and alteration of ion distribution across the myocardial cell membrane. The literature reviewed seemed to suggest that phenothiazines be used in only moderate dosages and that patients be monitored electrocardiographically. When Q-T prolongation occurs, the agents should be discontinued or the dosage reduced. Ventricular arrhythmia, if it occurs, responds to antiarrhythmics, cardioversion or a pacemaker.

REFERENCES

1. Moyer JH, Kent B, Knight R, et al: Laboratory and clinical observations on chlorpromazine hemodynamic and toxicological studies. Am J Med Sci 227:283-290, 1954

2. Schoonmaker FW, Osteen RT, Greenfield JC: Thioridazine (Mellaril®)-induced ventricular tachycardia controlled with an artificial pacemaker. Ann Intern Med 65:1076-1078, 1966

3. DeSautels S, Filteau C, St-Jean A: Ventricular tachycardia associated with administration of thioridazine hydrochloride (Mellaril)—Report of a case with favourable outcome. Can Med Assoc J 90:1030-1031, 1964

4. Liebaldt G: Suicid mit Chlorprothixen—Morphologische Befunde und Versuch ihrer physiologisch/chemischen Interpretation. Arzneim Forsch 14(suppl):596-598, 1964

5. Kelly HG, Fay JE, Laverty SG: Thioridazine hydrochloride (Mellaril)—Its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. Can Med Assoc J 89:546-554, 1963

6. Hollister LE, Kosek JC: Sudden death during treatment with phenothiazine derivatives. JAMA 192:1035-1038, 1965

7. Giles TD, Modlin RK: Death associated with ventricular arrhythmia and thioridazine hydrochloride. JAMA 205:108, 1968

8. Leestma JE, Koenig KL: Sudden death and phenothiazines—A current controversy. Arch Gen Psychiatry 18:137-148, 1968

9. Wendkos MH: Electrocardiographic effects of marihuana (Letter to the editor). JAMA 226:789-790, 1973

10. Ban TA, St-Jean A: The effect of phenothiazines on the electrocardiogram. Can Med Assoc J 91:537-540, 1964

11. Graupner KI, Murphree OD: Electrocardiographic changes associated with the use of thioridazine. J Neuropsychiatry 5:344-350, 1964

12. Huston JR, Bell GE: The effect of thioridazine hydrochloride and chlorpromazine on the electrocardiogram. JAMA 198: 16-20, 1966

13. Alexander S, Shader R, Grinspoon L: Electrocardiographic effects of thioridazine hydrochloride (Mellaril). Lahey Clin Found Bull 16:207-215, 1967

14. Burda CD: Electrocardiographic abnormalities induced by thioridazine (Merraril). Am Heart J 76:153-156, 1968

15. Wendkos MH: Cardiac changes related to phenothiazine therapy, with special reference to thioridazine. J Am Geriatr Soc 15:20-28, 1967

16. Wendkos MH: The significance of electrocardiographic changes produced by thioridazine. J New Drugs 4:322-332, 1964

17. Landmark KH: Kardiale virkninger av fenothiazinderivater. Nord Med 83:617-620, 1970

18. Alvarez-Mena SC, Frank MJ: Phenothiazine-induced T-wave abnormalities—Effects of overnight fasting. JAMA 224: 1730-1733, 1973

19. Peele R, von Loetzen IS: Phenothiazine death—A critical review. Am J Psychiatry 130:306-308, 1973

20. Richardson HL, Graupner KI, Richardson ME: Intramyocardial lesions in patients dying suddenly and unexpectedly. JAMA 195:254-260, 1966

21. Reinert RE, Hermann CG: Unexplained deaths during chlorpromazine therapy. J Nerv Ment Dis 131:435-442, 1960

22. Alexander CS, Nino A: Cardiovascular complications in young patients taking psychotropic drugs—A preliminary report. Am Heart J 78:757-769, 1969

23. Alexander CS: Cardiotoxic effects of phenothiazine and related drugs (Editorial). Circulation 38:1014-1015, 1968

24. Sharma RL, Arora RB: Antiarrhythmics XII—Antiarrhythmic activity of some phenothiazine derivatives in experimental cardiac arrhythmias. Indian J Med Res 49:1099-1112, 1961

25. Madan BR, Pendse VK, Antiarrhythmic activity of thioridazine hydrochloride. Am J Cardiol 11:78-81, 1963

26. Greiner AC, Nicolson GA: Pigment deposition in viscera associated with prolonged chlorpromazine therapy. Can Med Assoc J 91:627-635, 1964

27. Zelickson AS: Skin pigmentation and chlorpromazine. JAMA 194:670-672, 1965

28. Myocardial lesion pattern observed with phenothiazine therapy. Medical news. JAMA 202:27-28, 1967

29. Davis PW, Brody TM: Inhibition of Na^+-K^+-activated adenosine triphosphatase activity in rat brain by substituted phenothiazines. Biochem Pharmacol 15:703-710, 1966

30. Moore MT, Book MH: Sudden death in phenothiazine therapy—A clinicopathologic study of 12 cases. Psychiatry Q 44: 389-402, 1969

LETTERS *to the Editor*

Drug Combinations in Topical Therapy

To the Editor: The pages of The Western Journal of Medicine are, in my opinion, equal to those of any medical journal in respect to the wealth of useful information they contain. The article on "Synergism and Antagonism Among Antimicrobial Drugs" by Ernest Jawetz (West J Med 123:87-91, Aug 1975) and the Editorial: "Combination Antimicrobial Therapy" by Robert G. Petersdorf (pp 135-136 of the same issue) reinforce my opinion. Therefore what I write regarding these contributions is an addendum and in no respect an adverse criticism.

As so often, skin conditions differ from conditions in the viscera, blood stream, etc. It is a rule to find that skin diseases are caused, prolonged or aggravated, not by a single causal or contributory factor, but by several different pathogenic influences including several different kinds of microbes. Because the skin is colonized by many kinds of microbes and exposed to a constant rain of others, it is not unusual for skin lesions to be caused, maintained or aggravated by combinations of two or more of the following: staphylococci, streptococci, fungi, yeasts, diphtheroids, even virus, concurrently or in sequence. Treatment often must be given without sorting out or before sorting out the casual and contributory micro-organisms by microbiologic methods. Therefore, topical medicaments that exert antimicrobial action simultaneously on several different kinds of micro-organisms are likely to prove most effective in the majority of cases. Sometimes a single drug can exert such across-the-board antimicrobial action; sometimes a combination of two or more antimicrobial drugs is most likely to be beneficial. This is one of the reasons for using combination topical therapy in many dermatoses. But it is not the sole reason. There are other good reasons not related directly to combined antimicrobial effects but to other combinations of beneficial activities. I have discussed some of these elsewhere. (Skin & Allergy News Vol. 3: Oct 1972 and Vol. 3: Nov 1972)

Marion B. Sulzberger, MD
San Francisco

A Health Professions Student Scholarship Program

To the Editor: A relatively new medical program has taken existence at the Ventura County General Hospital in Ventura, California.

Doctor Harvey M. Harris, originator and director, developed a five-week Health Professions Student Scholarship Program (HPSSP), for high school seniors and college freshmen students, showing interests in medical and paramedical occupations.

The HPSSP enabled fifteen students to be chosen from both public and private schools within the County of Ventura. I was fortunate in being selected as one of the fifteen student scholars. For the duration of five summer weeks, we entered into the world of medicine and were encouraged to explore, observe, and inquire into all phases of medical activity. We encountered life and death and all the dimensions connecting the two. Throughout the program, each student was assigned to alternate departments to observe surgery, obstetrics, emergency cases, autopsies and of course, the less dramatic events, although of equal importance, that occur daily throughout the hospital. Through participation in this program, we have a far greater understandng of what medicine is really like and whether or not the field of medicine is what we truly desire. It is the most valuable and informative five-week investment a student could make.

Each physician may well recall the point in time when he stood on the threshold of college and therefore evaluate instantly the enormous asset this type of program could have provided him. A brief example: probably all medical sources will stress the importance of upcoming physicians being expected to maintain good physical condition. A student of books only, cannot possibly realize the full meaning of such a statement, for he has not had the opportunity to accompany a physician during a typical work day. He has no real way of knowing the extreme long hours and arduous work required of the physician until he has stood beside him hour after hour.

As in most professions a medical student must,

out of necessity, choose his career blindly. The student who says, "I want to be a doctor," usually has only booklets and counselors to accommodate his inquiries. While such sources are indeed helpful, only fragments of knowledge can be obtained from them. The ultimate opportunity is to work at his chosen field; to be there, to see, to experience for oneself the reality of medicine.

At seventeen years of age, I was privileged to witness that which is otherwise unavailable to students until the third year of medical school. There is no way to measure the knowledge received from having participated in this program. I have gained such insight pertaining to the field of medicine that I feel absolutely confident in making a decision. And for me, that decision is to become a physician.

It is my sincere hope that physicians throughout the United States will recognize this program for the valuable concept it is, and perhaps apply a similar one to other areas. Future physicians will be indebted to you for years to come, as I am indebted to Dr. Harris and the staff at General Hospital, Ventura, California.

PERRY SANTOS
Senior Ventura High
Ventura, California

EDITOR'S NOTE: Subsequent to acceptance of the above letter by the JOURNAL, the author informed us that he had submitted it to several publications. It also has been accepted for publication by the *Journal of the American Medical Association.*

Physician Supply in California

TO THE EDITOR: The study, "Physician Supply in California" (Western Journal of Medicine 123: 250-253, Sep 1975), reports information that might mislead the reader. It suggests that there is no California physician shortage but instead only a physician maldistribution, the suburban areas growing most while the rural areas are static or contract in the ratio of doctors to population.

The fact to be remembered at all times is that in a free uncontrolled society, shortage in any commodity is always first shown by maldistribution.

For example, no one now complains about the shortage of barbers. However, if one eliminated 20 percent of all barbers evenly throughout in Los Angeles County, in a little while, Beverly Hills, La Canada and Granada Hills will still be close to saturated while Watts, Bell Gardens and Pacoima would have lost most of their barbers—since barbers will move to the most rewarding areas by preference.

Doctors will also choose the most satisfying place to work—urban high income areas—during a time of increasing shortage of doctors as we now have. Why should they choose a ghetto, or a low income rural area where the shortage permits them to practice in the affluent more rewarding areas?

R. R. MERLISS, MD
Beverly Hills

Continuing Medical Education in Smaller Hospitals

TO THE EDITOR: Dr. Block's prescription for continuing medical education (CME) programs in a small community hospital [123:154-158, August 1975] arouses mixed feelings.

The initial reaction is one of pride in his achievement, and commendation to his medical staff, for CME resources in a meaningful, accessible pattern. Particularly the specialty meetings, where limited attendance involved participants to their benefit. His reference list is a real service for all programmers.

Next came a feeling of déjà vu: hasn't all this been going on for years in community hospitals throughout the nation? At least since the Joint Commission for Accreditation of Hospitals (JCAH) started applying its Standard VI on CME to its surveys. Some staffs of very small, remote hospitals have even formed consortia for this purpose.[1]

Then came a sense of opportunities still to be realized. "Continuing education" is a concept of personalized learning for a professional career. Medical staff members should review their individual activities, to see where their time, money and effort have been invested, to discover their unmet needs, and to plan ahead for better activities. The annual report forms from the California Medical Association (CMA) and the American Academy of Family Physicians provide this opportunity. It will show a major time investment in reading, although many of us cannot keep up with our own subscriptions. The JCAH survey specifically recommends a hospital library, which may also include tapes, films and the Medical Skills Library.[2] To get more involvement from "guest speakers," have them consult and comment on presentations of local cases. If the team ap-

proach to hospital care is indeed a reality, nurses and technicians should also participate in conferences. Teaching is an opportunity for CME no matter where a hospital is located, for there are always paramedicals, patients and public to be informed. Medical students are available to practitioner-preceptors through year-round Family Practice electives and through the summertime CMERF-SCOPE [California Medical Education and Research Foundation-Student Community Orientation and Preceptorship Education] project.

Penultimately, a word about the patient care audit. It is not advertised as the answer to CME programs, but as a logical way to help make CME programs relevant to medical practice. Current emphasis is because of its novelty and potential to education based on patient care. Effective use of audit, taking full advantage of each step, reveals this method to be an education in itself. Participation on an audit committee or in a staff ratification or report session can be basic CME. If an education program is additionally advisable, its content and methodology are evident. "Slavish adherence" to any method makes no sense, but neither does passive data transfer to an uninvolved audience. Keeping up with new facts may not be so important to practice as problem-solving techniques and appropriate use of existing services.

And finally to continuing staff education itself. Many part-time and full-time directors of medical education belong to a national organization, the Association for Hospital Medical Education (AHME), which provides ideas, experience and guidelines for hospital CME. Consultation on programs can be directly from the the CMA and its accreditation program, or from the AHME[3] through its regional representatives. Principles of CME apply to all community hospitals, small and large. The focus remains on individual practitioners, their learning styles and their needs for patient care.

JAMES H. THORPE, MD
Director of Medical Education
Sutter Community Hospitals
Sacramento, CA

REFERENCES

1. Zuckerman SL: Tri-hospital associations. AHME Journal 5: 29, 1972
2. Medical Skills Library, 12 categorical films designed by the American College of Physicians, and sold by ROCOM, Nutley, NJ 07110
3. Association for Hospital Medical Education (AHME), 1911 Jefferson Davis Highway—Suite 905, Arlington, VA 22202; phone (703) 521-1133

Gonococcal Arthritis

Because of the increase in the late diagnosis of gonorrhea, gonococcal arthritis is becoming a problem. At the University of Washington in 103 cases of undiagnosed arthritis, 25 percent had probably disseminated gonococcal infection. Pharyngeal infection and menstruation appeared to be associated with the dissemination of the infection to the joints. And this is a pretty typical kind of arthritis . . .

—ROBERT A. H. KINCH, MD, *Montreal*
Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 21, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Information

Refer to: Guidelines for the interview and examination of alleged rape victims—A conjoint effort of the California Medical Association Committee on Evolving Trends in Society Affecting Life, and the Advisory Panels of Obstetrics and Gynecology, Pathology, and Psychiatry of the Scientific Board of the California Medical Association. West J Med 123:420-422, Nov 1975

Guidelines for the Interview and Examination of Alleged Rape Victims

A conjoint effort of the Committee on Evolving Trends in Society Affecting Life, and the Advisory Panels of Obstetrics and Gynecology, Pathology, and Psychiatry of the Scientific Board of the California Medical Association.

THE ACT OF RAPE is perhaps one of the most psychologically devastating encounters a person can experience. It is a brutal act of violence which frequently robs its victims, whether male or female, of self-identity and carries ramifications of guilt and fear which are felt long after the patient leaves the emergency room. Therefore, the manner in which the medical treatment of the alleged rape victims is performed is of overwhelming significance to the psychological well-being of the patient. Gentle, sympathetic medical care can help lead to the recovery of self-identity and emotional health.

The following guidelines, prepared in response to Resolution No. 221-74, approved by the California Medical Association's House of Delegates, represent an attempt by the Association to express concern over the plight of female alleged rape victims and to call attention to the need to establish a psychological environment in health facilities which is conducive to sympathetic medical care. These guidelines cover four major aspects of the treatment of alleged rape victims: (1) psychological environment, (2) obtaining informed consent, (3) history and (4) examination.

It is recommended that each hospital medical staff develop its own protocol for the treatment of rape victims and make it available to all personnel in the emergency department. To the extent possible, procedures utilized in this protocol should include routine admission to hospital and access to social, legal and emotional counseling. Hospitals should provide staff training to assure compliance with the procedures and specific knowledge on the subject of rape. The establishment of a protocol will help to insure that all patients will receive the same level of care. Standardized recording procedures and terms, especially for the history-taking, should be included in the protocol. Procedures for appropriate referral, utilizing current referral lists for follow-up care to deal with any physical or emotional reactions should be established. The staff should be aware of the necessity for such follow-up care.

The legal responsibilities of the medical profession in treating an alleged rape victim vary among counties. For this reason, *it is recommended that physicians and hospitals consult their local authorities for the types of tests and specimens required as evidence and provide this information in written form as a part of the hospital's protocol for reference by health professionals.*

While the subject of rape is yet another area in which the medical and legal professions meet on rather hazy boundaries, it is the duty of the legal profession to determine whether or not a rape has actually occurred. With this in mind, the California Medical Association believes that all alleged rape victims should be approached gently and treated in an emotionally supportive manner by the medical profession. For purposes of sympathetic medical care, it should be assumed that a rape has actually occurred. To err on the side of sympathy is no failure. To err on the side of suspicion may help to insure psychological injury to a human being. It is worth emphasizing that rape is an assault and an aggression carried out sexually. The victim of rape is not a sexual partner and we need to be very careful not to imply that the person assaulted is a willing participant.

Psychological Environment

The emotional reactions of rape victims vary. One person may react hysterically; another may be stoic. One victim may be overwhelmed by questions; another may need extensive questioning to express her feelings. It is, at best, difficult

These guidelines were approved for publication by the California Medical Association Council, September 27, 1975.

Reprint requests to: Committee on Evolving Trends in Society Affecting Life, California Medical Association, 731 Market St., San Francisco, CA 94103.

to determine just what is meant by "emotional support." However, the assumption is that the patient has undergone a dehumanizing, emotionally shattering experience. Health professionals should accept the patient's reactions—whatever they may be. This air of acceptance often proves crucial to the patient's recovery. The way in which the physician takes the history and the gentleness, respect and thoroughness shown in the physical examination are in themselves therapeutic.

While the subjectivity of "emotional support" is recognized, it is recommended that the following guidelines be applied to all cases where rape is alleged:

- "Crisis intervention" should begin when the patient enters the health facility, and should not be relegated to follow-up psychiatric and community resources.
- The medical history and examination should be performed in a private area of the facility.
- If possible, the interview and examination should be conducted by a physician experienced in the treatment of rape victims.
- A sympathetic staff member, family member or friend (preferably female) should remain with the patient during the interview and examination to offer emotional support. This should be done only if the patient so desires.
- Care should be taken so that questions calling attention to the patient, such as "Where's the rape case?", or comments about the subject of rape are avoided in the public area of the facility.
- The treating physician should be aware of possible preexisting emotional problems in the alleged victim to determine the probability of the need for treatment of long-term ramifications.
- The patient should be urged to get immediate emotional support. The physician is encouraged to help the patient secure such support from resources available, including suggesting that she be accompanied by a friend or family member when leaving the emergency facility.
- The trauma of rape may carry long-term ramifications occurring months or even years after the incident. The patient should be made aware of the possibility of nightmares, psychosexual distress and other psychological disturbances. It is crucial that the physician assure the patient that such anxiety is natural and that appropriate supportive follow-up is available from professional and community resources.

Obtaining Informed Consent

Since the results of the medical examination may be used as evidence in the courtroom, obtaining informed consent for the examination is crucial. It should be determined at the outset whether or not the patient might bring her case to court. The patient has the right to request medical treatment only and to refuse examination for the collection of legal evidence. The patient should be informed, however, that in California, under the Health and Safety Code, hospitals are required to report cases of suspected assault and battery to the local authorities.

The concept of implied consent is applicable to any aspect of the interview and examination which is performed solely for the medical reasons. These aspects would include treatment for physical trauma as well as appropriate testing for pregnancy and venereal disease. Implied consent applies to any situation where the patient presents herself for treatment and to emergency medical treatment rendered when the patient is presented to the hospital by the local police.

It is recommended that the collection of legal evidence be encouraged, since the alleged victim may wish to report assault at some later date.

Any examination or laboratory test performed for evidentiary purposes requires a separate, specific, written consent. The patient should be informed of the Victim of Crime Indemnity Fund (California) which requires the local governmental unit to pay for the medical examination, if the examination is performed for evidentiary purposes.

Information gathered from the medical examination may *not* be released by the hospital without a signed and dated authorization from the patient for each separate release of information.

History

Adequate written history should be obtained. The history should include: (1) the length of time between the assault and the examination, (2) the manner of the assault (oral intercourse, anal intercourse, other sexual acts, degree of penetration, whether the male used a condom and whether the male ejaculated), (3) the date of the last menses, (4) use of birth control pills or intrauterine device (IUD), (5) the date and time the patient last consented to coitus, and (6) any significant actions subsequent to the alleged assault (showering, douching, changing of clothes or use of medications such as tranquilizers).

Examination

The examination should be preceded by a step-by-step explanation of the procedures the physician intends to perform.

Negative findings should be specifically noted as they are important in the legal evaluation of the medical record.

The record of the examination should cover the following elements.

1. There should be a general surveillance examination for any evidence of physical trauma. The general appearance of the patient should be noted and any bruises, lacerations and the like should be included.
2. The patient's emotional state should be observed and noted, using some objective scale or description.
3. Observation and notation of evidence of drug use, including alcohol, should be made using some objective scale. If so indicated by the patient's consent, blood, urine and gastric contents may be tested to determine the presence or absence of drugs in the body.
4. The condition of the patient's clothing should be observed and noted. Any suspicious moist or dried stains on the clothing may be used as evidence. If so indicated by the patient's consent, her clothing may be removed and given to the local authorities for evidentiary purposes.
5. The initial part of the gynecologic examination should be performed with a warm speculum. No lubricant should be used.
6. The police investigator should remain outside the examination room, unless otherwise specifically requested by the physician or the patient. It is recommended that any observer or assistant in the examination room be female.
7. At the minimum, the following tests should be performed and properly identified on vaginal pool material:
   a. swab, wet mount, acid phosphatase;
   b. dry smear;
   c. fixed smear.

   If so indicated, the following may also be collected:
   a. oral and rectal swabs and smears;
   b. separate smears for the vulva.
8. During the examination, legal evidence may be collected, if so indicated by the patient's consent:
   a. ten clipped pubic hairs or combings;
   b. appropriate photographs (taken by a female photographer, if possible);
   c. fingernail scrapings.

It is recommended that a checklist of appropriate tests, the necessary specimens and instructions for their handling be obtained from the pathology laboratory and made available in the examining room. The checklist should show the signature or approval from the district attorney and/or police department to document that it is in accordance with local legal requirements.

9. Baseline information for the presence or absence of gonorrhea and syphilis as well as less common venereal diseases should be obtained. The concept of "baseline information" should be explained to the patient and the need for retesting for the venereal diseases should be emphasized. Arrangements for follow-up retesting should be made at the time of the initial examination. Prophylactic treatment for gonorrhea and syphilis should be encouraged at the time of the first medical contact.
10. The presence or absence of pregnancy should be determined.
    a. Whether or not the patient was pregnant before the alleged assault should be determined by clinical evaluation and noted.
    b. The possibility of pregnancy as the result of the alleged rape should be discussed with the patient. Anti-pregnancy measures should be offered with a discussion of the risks and alternatives. Appropriate medical follow-up and counseling should be discussed on an individual basis.
11. Written information about venereal disease and pregnancy, as well as appropriate social and legal agencies, should be given to the victim upon first contact.
12. The patient should receive an explanation of where the specimens will be sent and where the results of laboratory tests may be obtained.
13. It should be emphasized to the patient that further medical and psychological care are important and necessary.

in memoriam

ANDERSON, CARSTEN RUSSELL, Los Angeles. Died August 12, 1975 in Beverly Hills of epidermoid carcinoma, aged 71. Graduate of the University of Minnesota Medical School, Minneapolis, 1931. Licensed in California in 1935. Dr. Anderson was a member of the Los Angeles County Medical Association.

BISHOP, KATHERINE SCOTT, Berkeley. Died September 20, 1975 in Berkeley of arteriosclerotic cardiovascular disease, aged 86. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1915. Licensed in California in 1936. Dr. Bishop was a retired member of the Alameda-Contra Costa Medical Association.

EAGLESTON, FREDERICK LEROY, Palo Alto. Died August 8, 1975 in Stanford of heart disease, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1938. Licensed in California in 1951. Dr. Eagleston was an associate member of the Santa Clara County Medical Society.

FRANCOEUR, JULES ANDRE, Los Angeles. Died August 3, 1975 of heart disease, aged 42. Graduate of the University of Ottawa Faculty of Medicine, 1958. Licensed in California in 1969. Dr. Francoeur was a member of the Los Angeles County Medical Association.

GLICK, LOUIS JOSEPH, VALLEJO. Died September 16, 1975 of cancer, aged 66. Graduate of New York University College of Medicine, New York, 1935. Licensed in California in 1951. Dr. Glick was a member of the Solano County Medical Society.

HARRIS, TRESTER SMITH, Corona. Died September 21, 1975 in Hemet, aged 71. Graduate of Baylor University College of Medicine, Houston, 1936. Licensed in California in 1936. Dr. Harris was a retired member of the Riverside County Medical Association.

KATIBAH, EDMUND M., San Francisco. Died September 11, 1975 in San Francisco, aged 39. Graduate of Emory University School of Medicine, Atlanta, 1961. Licensed in California in 1965. Dr. Katibah was a member of the San Francisco Medical Society.

LEIDIG, LAWRENCE R., Santa Monica. Died May 10, 1975 in Santa Monica of heart disease, aged 79. Graduate of Baylor University College of Medicine, Houston, 1925. Licensed in California in 1927. Dr. Leidig was a member of the Los Angeles County Medical Association.

LEVIN, GRANT, San Francisco. Died September 23, 1975 in San Francisco, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Dr. Levin was a retired member of the San Francisco Medical Society.

LEVIN, MARCIA J., Sacramento. Died September 25, 1975 as a result of an automobile accident near Vallejo, aged 50. Graduate of Women's Medical College of Pennsylvania, Philadelphia, 1951. Licensed in California in 1953. Dr. Levin was an associate member of the Sacramento County Medical Association

LONES, FRANK ELWIN, Santa Rosa. Died September 14, 1975 in Santa Rosa of lymphoma, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr. Lones was a member of the Sonoma County Medical Association.

LUM, DONALD D., Alameda. Died September 16, 1975 in Alameda of myocardial infarction, aged 77. Graduate of Harvard Medical School, Boston, 1922. Licensed in California in 1923. Dr. Lum was a retired member of the Alameda-Contra Costa Medical Association.

OGDEN, RODERICK A., Bakersfield. Died September 11, 1975 in Bakersfield of cancer, aged 71. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr. Ogden was a member of the Kern County Medical Society.

TELFORD, PERCY K., Los Angeles. Died July 2, 1975, aged 87. Graduate of Indiana University School of Medicine, Indianapolis, 1911. Licensed in California in 1916. Dr. Telford was a retired member of the Los Angeles County Medical Association.

TERRY, CHARLES TAYLOR, Long Beach. Died July 28, 1975 in Carson, aged 54. Graduate of Howard University College of Medicine, Washington, DC, 1946. Licensed in California in 1950. Dr. Terry was a member of the Los Angeles County Medical Association.

THOMPSON, HAROLD LINCOLN, Los Angeles. Died August 28, 1975 in Glendale, aged 78. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Dr. Thompson was a member of the Los Angeles County Medical Association.

TORNELL, ROBERT R., Los Angeles. Died April 24, 1975 of heart disease, aged 75. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1928. MD degree from California Colllege of Medicine, 1962. Dr. Tornell was a retired member of the Forty First Medical Society.

TYLER, EDWARD T., Los Angeles. Died July 30, 1975 of heart disease, aged 62. Graduate of Long Island College of Medicine, New York, 1938. Licensed in California in 1945. Dr. Tyler was a member of the Los Angeles County Medical Association.

WALLACE, WILLIAM EARL, Whittier. Died August 24, 1975 in Whittier, aged 80. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1920. Licensed in California in 1924. Dr. Wallace was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MICROBIOLOGY OF HUMAN SKIN—Volume 2 in the Series: Major Problems in Dermatology—W. C. Noble, PhD, MRC Path, Senior Lecturer, Institute of Dermatology, Head of Department of Bacteriology, St. John's Hospital for Diseases of the Skin, London; and Dorothy A. Somerville, PhD, Lecturer, Department of Bacteriology, University of Glasgow, Royal Infirmary, Glasgow. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 341 pages, $22.50.

This book proves to be a readable and exceptionally good review of the general bacteriology of the skin. It is perhaps less good for virology. However, it is to be commended for its readable style, and will carefully acquaint the beginner in an easy manner with the bacterial ecology of skin. It also serves as an inclusive and objective, well-documented reference source through 1972. If one were to look for drawbacks, the subject of gonococcal infections is somewhat skimpy, and falls somewhat short of the standards set elsewhere in the book, restricting itself to European literature. There is relatively little attention accorded virus and mycoplasma with the exception of citation of some reviews, and for the clinician the herpes virus and varicella-zoster virus segments get relatively little attention. In sum, this is really a scholarly update of information described in Dr. Marples' monumental contribution on the ecology of the skin. It is a good book for anyone interested in the field of infectious diseases. It should be highly relevant to the needs of dermatologists and burn surgeons, and should be a useful reference work for hospital microbiologists and public health officials.

GEORGE F. ODLAND, MD

* * *

BENEFICENT EUTHANASIA—Edited by Marvin Kohl, PhD, Professor of Philosophy, State University of New York College at Fredonia. Prometheus Books, 923 Kensington Avenue, Buffalo, NY (14215), 1975. 266 pages, $10.95 (Cloth); $4.95 (Paperback).

Beneficent euthanasia means a good death—it is mercy killing as a clinical act of justice and kindness. This statement expresses the primary issue of the book. Although it is filled with rhetorical debate that stretches the rationality of any clinician it does touch all of the issues.

Each physician-reader of this review has encountered clinical demands generating a personal and lonely anguish with the challenge of euthanasia. He has found himself coerced by the availability of advanced technology to prolong the lives of those horribly and irreversibly deformed at birth, blasted by trauma or dying in terminal forms of chronic illness. There comes that moment when a physician ponders whether it would not be more merciful to assist actively in bringing about a peaceful, painless and dignified death. The question arises, why go one step further? Then begins his inner dissonance that explores the human issue: it is immoral, it is murder. Moreover it is a criminal act and I have no legal protection. To offer drugs for a suicidal act constitutes the same intention. Even with fully informed consent and cooperation, may not its authenticity be open to future question? Is it right for me to put my rationality over the moral and legal codes? In the end no one can decide for me nor do it for me. I am alone. I alone am responsible.

The book proposes and delineates hundreds of variations of both the objective and subjective conditions attending the euthanasia movement (now called "deliverance"). The primary theme is stated by the protagonist and editor (Kohl) and debated by the contributors in 20 well categorized and skillfully arranged chapters backed up by a useful appendix and a good annotated bibliography. These 20 contributors (ten philosophers, three theologians, three lawyers, three physicians and one nurse) are all academicians—but don't let this array turn you off, for the clinician needs his homework on value systems properly done by scholars. The theme of the book can be stated: "As long as we respect human dignity and regard kindly acts as being at least virtuous, beneficent euthanasia, or mercy killing, will be practical and remain a moral activity." Euthanasia here means "the allowance or inducement of as quick and painless a death as is possible."

Antagonists to the theme counter that all human life is intrinsically good. The editor responds: How can that be, "when a life has been irretrievably blasted by an accident or blighted by some ghastly illness, or when all dignity, beauty and meaning have vanished?" To support life then as intrinsically good "entails pointless suffering and to support it is not kind nor just." For the borderline cases the criteria of kindness continues: "If there is a reasonable doubt that the supported act is not kind or not the kindest possible alternative, one should refrain from acting."

Because this book is relevant and timely I recommend that practicing physicians study it. Knowing in addition that it would be of value to the busy housestaffs of our community hospitals who find themselves frequently encountering these problems but whose training demands allow little time for background reading or freedom for debate let me try to paraphrase the arguments contained herein: (1) fundamental Jewish truth holds that morality cannot be derived from reason—it is a given. Murder then is a violation of God's law and we must not kill the innocent and righteous. Therefore acts of beneficent euthanasia are never directly permissible. (2) The Jesuit contributor argues that there is vigorous debate among Catholics that all ethics assess the moral significance of the situation being judged and in certain cases direct positive intervention to bring death may be morally permissible. (3) A more modern ethicist (Fletcher) would drop completely the sanctity of life ethic and embrace a quality of life ethic, insisting that Christian ethics are based on love not on the law. He feels the heart of human responsibiity is to respond—to human needs. The rightness or wrongness of euthanasia depends on the situation and that situation needs to be studied for the proper response like any other clinical situation. (4) Traditional social morality sets its face against suicide, but it is argued here that in some cases this is ethically justified—especially when life itself is no longer meaningful and its purpose no longer self-sustaining. It is not life itself that is worth living but the "good life." Certain deformed modes of life are more insulting to dignity than any suicide could possibly be. Throughout the discussion there is universal agreement in one area—the question of consent. A fully informed and

freely given consent (that is not transferable) is unarguably a necessary and primary condition.

The most controversial area surrounds the issue of legalization. The proposition is advanced that if a physician acts benevolently to benefit his patient and if the patient voluntarily consents or requests it (or both), there is no reason why the law should not legalize the physician's killing his patient. There is at present, of course, no such law. Nor are the prospects imminent. Drafting such a law would be difficult because man's motives are suspect: legalized euthanasia could unfortunately be generalized (to get auntie out of the way because she is a burden). In England, a first attempt was made in 1969 in a proposed House of Lords bill. The bill requested 30 days consent before the act. It would allow a patient the means to end his own life and a nurse to act on the direction of a physician. The 30-day consent period was later amended to 60. Voting on the bill was 40 pro and 60 con. Although no legislation is presently underway, there is general agreement that the heart of any law to make euthanasia morally or legally permissible should be fully informed consent (and all variations on this are acknowledged and discussed). To a concerned physician, the dangers of legalization are clear. Laws erode freedom and give power. The prospect of a "physician-technician" approved by statute, functioning as a "deliverer" (the euphemistic term employed here) is one that few of us can view with equanimity.

The book ends with a formal petition and plea for beneficient euthanasia signed by 47 outstanding world scientific and cultural leaders—there are three Californians: Dr. Pauling at Stanford; the Rev. Pett at Glide Memorial Church, San Francisco; and Dr. Leake at the University of California, San Francisco.

Perhaps the reviewer should commit himself: I believe in the social possibility of beneficent euthanasia with the proviso that there be informed consent but moreover that it be generated in the heart of a concerned clinical partnership where physician and patient mutually trust and know one another.

H. Harrison Sadler, MD

* * *

THE COURAGE TO FAIL—A Social View of Organ Transplants and Dialysis—Renée C. Fox, Professor and Chairman, Department of Sociology, University of Pennsylvania, and Professor of Sociology, Departments of Psychiatry and Medicine, University of Pennsylvania School of Medicine; and Judith P. Swazey, Associate Professor, Socio-Medical Sciences Department, Boston University School of Medicine. University of Chicago Press, Chicago, Illinois (60637), 1974. 395 pages, $12.95.

Here is a book which quietly and persuasively sounds an alarm. It is called *The Courage to Fail,* after the affirmative mode of Tillich's *Courage to Be.* The subject of this book is the prolongation of life through the use of the technologies of renal dialysis, heart and kidney transplantation—often called "half-way" technologies because of their limitations. It explores first hand the problems of scientific uncertainty (immunological), the meaning of life and death, the impact of scarcity and choice, and the interventions by scientific man into a natural human condition—chronic disease. This intervention is possible as a consequence of the momentum of medical science evolving these technologies. Their clinical applications create a bio-medical frontier where the existing social status quo and the institutional norms of law, ethics, morality and economy are challenged. Such a challenge requires an increasing public participation in chartering a new course. It is these therapeutic innovations and this "new biology," or the frontier, which require the particular courage to probe—and often to fail.

The authors are mature and seasoned social scientists and teachers: Renée Fox is the Chairman of the Department of Sociology at the University of Pennsylvania School of Medicine, and Judith Swazey is an Associate Professor of Socio-medical Science at Boston University School of Medicine. They set forth their account in a journalistic rather than a scientific fashion, but this should not deter the thoughtful reader for here in one comprehensive and highly readable book are portrayed all the characters and events of this frontier field set in the framework of technical achievement and social conscience. The contents, for instance, include: a broad panoramic overview of the dialysis and transplant innovations and a conceptualization of the "courage to fail ethos"; an intimate, almost eavesdropping, evaluation and interviews with and of the scientific innovators themselves: Barnard, Cooley, DeBakey in the heart transplant field, and the poignant views of Scribner whose pioneering work with renal dialysis and the invention of the plastic cannula which made it all possible. They present the broad social perspective, "the common conscience" of society, the view, for example, that our organs might be viewed and claimed as a potential social commodity. In the center ring at all times is the ever present paradigm of the renal dialysis, heart and kidney transplant *model* which exemplifies the attributes and processes of these therapeutic innovations on the frontier, and their impact on society.

To dramatize how these issues impinge upon actual cases, the authors focus on two in particular: that of the artificial heart and that of Ernie Crowfeather. In the first case, that of the artificial heart, a Mr. Karp received a mechanical heart and after his death, Mrs. Karp alleged negligence and claimed the lack of informed consent and the presence of improper experimental controls (the mechanical device had not received sufficient clinical trials in animals). The entire court procedures are included as well as intimate interviews with the "pump team."

The second case is that of Ernie Crowfeather. He was an American Indian by ancestry though not by personal identity, who lost his first kidney following a bicycle accident. The remaining kidney later became infected and he moved inevitably into the health delivery system where for the next thirty months, at the cost of an estimated $100,000, his life was prolonged. He cared little for himself, never followed the therapeutic regimen and even while rejecting his kidney, was in and out of jail. Finally he died alone in a motel (suicide), even while his doctors rushed there to save him. One physician asked the anguishing question, "What was the meaning of his life?"

Moving beyond these specific cases and considerations, however, the authors focus their attention and concern on the larger issue raised in this work. In particular, they point to the challenge it poses to the physician's privileged status—that of the sole arbiter of health care. This challenge arises out of recognizing the human and social phenomenon of chronic illness, so well illustrated here with the kidney and heart model. More and more the thoughtful physician is recognizing the necessity of replacing the illusion of cure in these cases with the reality of a lifetime management program. He cannot turn away from the unbelievable complications arising from these programs, the terrible limitations on the quality of life, the marginal personal existences and enormous costs. The public, however, has not yet come to this recognition and still approaches the physician with the expectation of a "cure," or at least a greater measure of freedom. On this clinical frontier then, arise the deep

probing questions which demand greater physician sophistication and more public participation. The authors pull no punches in presenting them. On page 324 they list a dozen related questions among which is "should physicians invariably be required to do everything they can to treat dying patients?" With the popular demand for the "right to health care" even these two familiar terms, "health" and "care," require a more thorough examination and increasing colloquy and commitment.

The reader in a hurry will find the two case studies (chapters 7 and 10) rewarding. For one with more leisure, a look through the excellent index and bibliography is highly recommended. If in addition you are approaching a political or academic interest and want more data, read J. Katz' and Capron's *On the Social Factors Affecting the Modern Treatment of Catastrophic Disease* (National Center for Health Service, Dept. HEW, Contract No. HSM 110-69-213). Don't, however, pass it by. These authors have sounded an alarm of importance to all physicians and we would do well to heed it.

H. Harrison Sadler, MD

* * *

FITNESS, HEALTH, AND WORK CAPACITY: International Standards for Assessment—Editor: Leonard A. Larson, PhD, Director of the Department of Physical Education for Men, University of Wisconsin, Madison. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1974. 593 pages, $14.95.

This volume is written primarily for the physician interested in sports medicine or physical education and various para-medical personnel involved in these fields. It contains statistics and methods of examination in connection with evaluation of physiologic measurement, physique, and performance of individuals particularly directed toward various forms of athletics. This material has been gathered by the International Committee for the Standardization of Physical Fitness Tests, over the past ten years. Its various chapters and sections are written and supervised by members of this international committee. The book is well written and well organized but as a result of multiplicity of authors, there is unavoidable repetition. For example, the explanation of physical examination in this field is repeated at least four times.

The section on anthropologic measurements and body compartmentation is extremely detailed and contains much useful information. Likewise, the section on measurement of physiologic factors and performance factors contains much useful detail which should be of great value not only to those interested in sports medicine but to persons specializing in physical medicine, neurology and orthopedics.

On reading the book, one gains the impression that there is an attempt to "socialize" this branch of medicine in order to select and predetermine skills in various sports depending on body build, power, nationality, race, environment, personal status and motivation. It is obvious to those of us who saw the small and chunky Bill Carr defeat the lanky, more ideal statured Ben Eastman in the 1936 Olympics, that this is a commendable aim but that it will be many years before a laboratory can predict the winner of a race in highly competitive athletic events. Obviously, psychologic factors which enter into these functions are not readily measurable and many of these psychologic factors are unpredictable (i.e., why do various athletes in relatively measurable sports, such as baseball, pitching and batting, have such a variation between their "good" and "bad" days?).

The very interesting equipment for measuring the strength of various muscle groups and the comparative strengths of muscle groups in various sporting events, makes interesting statistics. However, there is no explanation of the day to day change in the strength of muscle groups in individuals which may be a factor in the performance of their various events on particular days.

The subject covered by this book is an extremely complicated one and difficult to categorize. I believe the committee has done an outstanding job in this direction and has helped in the understanding of physical performance and work capacity in sports. This book should find itself on the shelves of all medical libraries and in the libraries of Physical Education departments and sections of Physical Medicine and Physiology. It is an invaluable reference book.

James H. Thompson, MD

* * *

MICROORGANISMS AND HUMAN DISEASE—Ernest Alan Meyer, ScD, Professor of Microbiology, Department of Microbiology, University of Oregon Medical School, Lecturer in Microbiology, University of Oregon School of Nursing. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1974. 451 pages, $15.00.

Microorganisms and Human Disease is intended for "students preparing for medically oriented careers," though the author indicates it may also prove useful to others already in the health sciences. It is apparent that the references provided, many published as recently as 1973 are more appropriate for those who are more sophisticated in microbiology and infectious disease.

The book is divided into five parts: An Introduction to Medical Microbiology, Bacteria and Human Disease, Viruses and Human Disease, Fungi and Human Disease, Parasites and Human Disease. There is considerable unevenness in the treatment given various sections or subsections. For example in the chapter "Antimicrobial Methods" dealing with antiseptics and disinfectants as well as chemotherapeutic agents, the only structural formulae shown are those of sulfanilamide and p-aminobenzoic acid. No structure of the antibiotics is shown which could permit appreciation of certain of their properties, for example, the susceptibility of penicillin G to destruction by beta-lactamase. On the other hand a half page is devoted to a hoary depiction of bacterial colonial morphology. There is virtually no description of physiology or metabolism so important in identification of bacteria. Extensive attention is given to the protozoan, and helminthic agents (127 pages) whereas only 42 pages are devoted to virology. A short section on the common cold fails to name specifically any of the etiological agents, for example, rhinoviruses. Bacteria are dealt with in a helpful format that includes classification and identification, pathogenesis, disease characteristics, diagnosis, and others, but this format is inexplicably applied erratically to other agents.

Some sections are misleading, incorrect or incomplete. For example, one might infer that synthesis of "penicillanic acid" is usually carried out without the essential biological role of a Penicillium. Cephalosporins are not mentioned. The section on immunology and host-parasite interaction is extremely brief (9 pages). Anachronistically there is a half page devoted to the Schick test. Mentioned with the Coombs' test is the unexplained "incomplete antibody." Tuberculosis is presented as an infection of lung or intestine. Gonorrhea in the adult female is described only with reference to the large proportion of asymptomatic cases.

The type is large and readable. Review questions and answers represent a useful study device for some students. However, illustrations are not numerous and are generally of poor quality except those in the section on

parasitology that contains many and good line drawings from other treatises on parasitology.

This reviewer feels that publishers too should exact a more critical review before committing a text to the press. The author has tried valiantly to provide an inclusive text but it is not adequate for medical or paramedical personnel nor for students preparing for such careers.

DEMOSTHENES PAPPAGIANIS, MD, PH D

* * *

THE EFFECTS OF HOSPITALIZATION ON CHILDREN—Models for Their Care—Edited by Evelyn K. Oremland, MSW, and Jerome D. Oremland, MD, Faculty, San Francisco Psychoanalytic Institute, Chairman, Extension Division, Psychoanalytic Institute. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill (62703), 1973. 360 pages, $12.75.

The title of the book summarizes its contents and goals. It is based on a report of a symposium in which an impressive group of contributors from various disciplines participated. Dr. Solnit's opening address serves as the core of the book. In it he stresses the importance of careful selectivity in the choice of procedures because methods of approach and care, useful under some circumstances, may not be so when applied in the instance of hospitalized children, and may even prove detrimental. Increasingly narrowed specialization, scientific and technological advances are inevitably accompanied by dehumanization and depersonalization which increase susceptibility to psychological damage and make hospitalization more difficult for children to endure. It is commendable that due consideration is accorded the importance of developmental levels in relation to the child's capacity to deal with the hospital experience because such capacity undergoes changes with ego growth, establishment of defense mechanisms and mastery.

The need for preparation, proper timing of elective surgery and appropriate atmosphere in the hospital are all stressed in order to avoid reactions, immediate or delayed. A post-surgical program which permits working through the trauma of the surgery or hospitalization has proven desirable.

In the chapter "The Infant in the Hospital," Dr. Calvin F. Settlage presents a concise summary of psychoanalytic principles especially in relation to developmental phases. This is followed by some observations on early mother-child interaction, and the effects of hospitalization and separation on both infant and mother in the interval from birth to two years.

The book describes the special needs of adolescents in their period of transition from childhood to adulthood, and the ways in which hospitals may meet such needs. Here, too, developmental assessment rather than chronological age should be the determinant in many decisions relating to disposition and procedures, with flexibility the key to the still unsettled personality.

The section on psychological implications of transplants in children deals with touching situations in the lives of children who suffer renal failure, and their families. The relationship between them and the surgeon, and his willingness to respond to their inquiries are important. The staff also needs help in dealing with these patients and their families, and their anxieties. Several unforeseeable psychological implications and complications are discussed in detail, as well as those decisions concerning which family and patient need help. Questions of medical ethics and values, nonexistent in the pretransplant era, now present themselves for contemplation and judgment. This part of the book was the most interesting for me.

The chapter on the dying child stresses the need to appreciate changing developmental patterns so as to permit and even aid the child to talk about death and to ask questions about matters which he finds puzzling, and to feel reassured that he may speak freely of eventualities that many parents are unable to face. Reactions of the staff are discussed and some recommendations made to facilitate their tasks, and protect the child in such painful circumstances. Included is a moving and informative account of the experiences of a dying child and a psychologist who served as "play doctor" and coordinator for the family and caretakers.

The book also addresses itself to "Hospitalization as a Psychological Growth Experience." Ministrations which bring about a cessation of pain and symptoms, feelings of worthiness enjoyed by the child because he is the recipient of special attention, mobilization of the family around his acute needs, and the sense of mastery over the crisis of hospitalization, all have positive value. Another important use of the hospital is as a haven for children while destructive family problems and crises are being resolved. It is concluded that an interested, compatible, coordinated, interdisciplinary team can minimize the adverse effects of hospitalization on children and maximize its benefits. The ideal team is perceived as functional, nonauthoritarian and nonhierarchial; the reader is cautioned about difficulties which may beset the team. Arguments in favor of Children's Hospitals for children, despite their costliness, are presented.

The book begins promisingly with Dr. Solnit's remarks. However, with such a wide variety of contributors, a uniform quality of presentation cannot be insured, and some of the articles prove disappointing. Anticipated answers are not forthcoming, possibly because insufficient time has elapsed to permit accumulation of adequate scientific and validated data. As Dr. Errante says, "The teams must develop more scientifically. Theory and anecdotes do not provide a solid enough base for major changes in health care organizations."

The number of individuals and specialties included in the team becomes overwhelming, and the very inconsistencies and fragmentation which it seeks to abolish become inevitable accompaniments of its existence. Perhaps one of the important purposes served by the book is its presentation of a model, albeit diffuse and too inclusive, to serve as a prototype to be chipped and chiseled into a wieldy, practical and useful entity.

I recommend the book to all who participate or have an interest in the care of children. It is informative and provocative, reads pleasantly and easily and represents the best thinking available at present.

HELEN TAUSEND, MD

* * *

HEROIN ADDICTION IN BRITAIN—What Americans Can Learn from the English Experience—Horace Freeland Judson. Harcourt Brace Jovanovich, Inc., 757 Third Avenue, New York City (10017), 1974. 200 pages, $6.95.

I read Horace Judson's book *Heroin Addiction in Britain: What Americans Can Learn from the English Experience,* with enthusiasm and anticipation. Unfortunately, I was somewhat disappointed after completing the book. My enthusiasm was generated by the fact that I had read his previous articles on the British system of heroin maintenance which were published in *The New Yorker* in September-October of 1973 just prior to a Drug Abuse Council sponsored trip that I took to England. I found at that time, that his writing style was typical of science writers and extremely informative. The articles that he wrote in *The New Yorker* were excellent preparation for my visit to England and my tour of their

heroin maintenance facilities. Regrettably, this book did not add as much to his *New Yorker* articles as I had hoped and I found his writing style to be somewhat less objective and slightly more pedantic. Given these limitations and biases on my part, I still believe that this would be a valuable book for physicians interested in drug abuse to read, although unfortunately it offers relatively little new data, but rather is a compilation and clarification of existing information. However, I have found that the "British system" is often bandied about in the United States at a variety of levels—from the federal policy level to the legislator to the general public—and is very often quite confused and misinterpreted. Mr. Judson's interesting historical view and detailed analysis will help clarify exactly what the British system is and possibly help us learn from it, particularly in relationship to the hotly debated proposal as to whether we should introduce legal heroin maintenance clinics in the United States.

His style was narrative and his method was essentially interview and observation, which may be viewed as somewhat confusing and unscientific to many physicians. Unfortunately, too much of the literature in the drug abuse field is this style, but often a good science writer can communicate to physicians better than a medical scientist, and I am not overly critical of the book on these terms. The pharmacology in the book was relatively weak and condescending as if he wrote it for the layman, but I found the historical view of heroin to be quite interesting, particularly in relationship to its former place in medical practice—something that many if not most physicians in the United States have forgotten. He reemphasized the truism that pure heroin is not nearly as dangerous as most people think, particularly when administered orally as a cough syrup or taken by routes of administration other than that of injection. In addition, he pointed out that the development of the heroin maintenance system in England came out of an essential medical and social model and did not have the aura of hysteria and prevention of drug related crime which has so dominated our heroin policy in the United States. Of greater interest, physicians have had a much better relationship with addicts in England and have been much more involved in their care than have their cohorts in the United States, who for the most part, have shunned responsibility for the treatment of the drug abuser. Certainly, one of the reasons that we have not done a better job with drug abuse in the United States is the lack of medical involvement on the part of the physicians in our country. Comparison with our English physician cohorts makes us look unresponsive and rather inadequate in the addiction field. It is this, which I believe is his strongest point, that Judson repeats several times in several ways, both by himself and through selective quotes from doctors he interviewed, including such leading drug experts in England as Dr. Martin Mitcheson and Dr. Griffith Edwards.

The size of the heroin problem in England is much smaller than that of the United States and is much less diverse. In my opinion, Judson stretches too far on occasions to make correlations between our two problems, but such correlations did not influence his many valuable conclusions, particularly in relationship to improving our understanding of the basic properties of heroin maintenance, some of the problems we will run into if heroin maintenance is initiated in the United States, and the great need to expand medical community involvement in the drug abuse problem. As Dr. Martin Mitcheson said on page 87, " . . . unlike your American street junkies, our addicts have always been doctor-oriented." This is not as much a property of the addict himself, but a reflection of the attitude of the treating physician and the inadequacies and unresponsiveness of our health care delivery system in the United States to properly relate to the problem of drug abuse in America.

The epidemiological descriptions of other mini drug epidemics in England was also a strong point in Judson's book. The epidemic of injectable methamphetamine in 1968 which existed in London was quite analagous in certain characteristics to the speed scene which dominated areas like the Haight-Ashbury district of San Francisco during a corresponding period. It is both a mystery and a subject of great interest how the youth drug culture gets involved with similar drugs at the same time in areas as far apart as London and San Francisco, and Judson gives some interesting, although limited and relatively superficial, explanations of this similarity between worldwide youth drug culture patterns. Hopefully, such observations will stimulate scientists to do more research in the important areas of drug abuse epidemiology. Judson also offers some interesting speculations and observations on the development of America's drug abuse industry and the politics which seem to dominate so many of our drug decisions, many of which are born out of hysteria and political expediency, rather than humanistic concern for the patient and rational disciplined medical thought. I also found his somewhat detailed cost analysis of a heroin maintenance clinic in England offers some practical guidelines for heroin maintenance if it is instituted in the United States.

In general, I found this book to be interesting and informative, despite its limitations, and I would recommend that physicians and other health professionals interested in this important subject to acquaint themselves with the valuable descriptions and insights contained in *Heroin Addiction in Britain: What Americans Can Learn from the English Experience.*

DAVID E. SMITH, MD

* * *

HANDBOOK OF PSYCHIATRY—Third Edition—Edited by Philip Solomon, MD, Clinical Professor of Psychiatry, University of California, San Diego, School of Medicine; and Vernon D. Patch, MD, Associate Professor of Psychiatry, Harvard Medical School, and Director, City of Boston Drug Treatment Center. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1974. 706 pages, $8.00.

The *Handbook of Psychiatry* is a softcover, 600-plus page book which attempts to cover many issues in the area of psychiatry and social science. The authors differentiate their handbook from a textbook or encyclopedia. They indicate that the handbook is intended for ready consultation, and is supposed to be a storehouse of information of current, practical importance, with emphasis on practice rather than theory. They state its chief function is "to aid the physician who faces a psychiatric problem and wishes to review relative material in the field."

In general, the handbook does meet these objectives. It is divided into four sections. Section One covers psychiatric background. Section Two covers psychiatric illness. Section Three covers psychiatric treatment. And Section Four covers special psychiatric fields.

A major deficiency in the textbook is too much emphasis on practice, without any attempt to provide a theoretical base. The chapter on psychoanalysis, which is included late in the book, does describe defense mechanisms which are acting in a number of psychiatric syndromes. These syndromes are discussed earlier on in the book. It would have been perhaps more appropriate in the first section of the book to include some general overview of the psychobiosocial thinking in psychiatry. Without this, the handbook can easily become a cookbook.

Clearly, this is not what the authors desire, but in their attempt to be practical, they have been too skimpy with providing a reasonable theoretical base.

The chapters on psychiatric illness are adequate, descriptive, and cover a great many clinical syndromes. As with any handbook of this size, there are areas of misinformation, or areas of minimal information. For instance, in the discussion of mental status examination, digits forward and backward is listed as the major simple memory test. Clearly, the authors mean this to be one of a number of tests which should be given, but for the handbook user it could appear that digits forward and backward is an adequate test of memory. Under such circumstances, cases of Korsakoff's syndrome would be clearly missed. There are similar deficiencies in defining endogenous depressions, and the meaning of the term "illusion."

The chapter on psychiatric treatment includes a detailed description of psychotherapy. This is a particularly useful chapter, since it gves a verbatim account of the kinds of interaction psychiatrists have with their patients. The chapter emphasizes the practice of psychotherapy, rather than theory, and does manage to place psychotherapy's importance within a medical framework.

The chapters on drug treatment are adequate, but some would question the implication that barbiturates are as effective as minor tranquilizers. The authors unfortunately make no distinction between the effectiveness and safety of ECT versus tricyclic anti-depressants. This gives the impression that they are equally effective, and that anti-depressants are probably a better way to treat a depressed patient. The psychopharmacological side effects are adequately covered.

It is doubtful whether the chapters on psychiatric social work and psychiatric nursing add anything substantial to such a handbook.

The chapters on special psychiatric fields seem adequate.

It should be noted that the book includes the most recent articles in literature, which are well documented at the end of each chapter.

As a handbook of psychiatry, this book will be of great use to medical students, interns, residents and practicing psychiatrists. Except for inaccuracies such as those previously described, this text fills a need for a handy, yet detailed, book which has up-to-date information for the person who needs to answer a practical question. In this regard, it meets the major objectives that the authors outlined at the beginning of the book.

DAVID E. RASKIN, MD

* * *

LUPUS ERYTHEMATOSUS—A Review of the Current Status of Discoid and Systemic Lupus Erythematosus and Their Variants—Second Edition—Edited by Edmund L. Dubois, MD, Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Director of the "Collagen Disease" Clinic, Los Angeles County/University of Southern California Medical Center, Los Angeles. University of Southern California Press, Los Angeles, CA (90007), 1974. 798 pages, $36.00 plus $1.50 shipping in the U.S. and 6% Sales Tax for California residents. (NOTE: copies or further information can be obtained by contacting the editor directly at the following address: Edmund L. Dubois, MD, Editor, 435 North Bedford Drive, Beverly Hills, CA 90210.)

It must be made very clear that *Lupus Erythematosus —Second Edition* does not herald the end of our national inflationary spiral by giving us 798 pages of textbook for $36. Rather, we have an artful interdigitation of eight-year-old chapters from the First Edition followed by Supplements that revise what has just preceded. This example of publishing legerdemain does not come off entirely successfully even from a visual standpoint with variation in type spacing, and blackness intensity on the same page suggesting that machines of similarly diverse vintage were at work on the same surface.

The advantages of this novel arrangement are pointed out in the Preface and include, beside production economy, the ability to compare newer and older information and a shorter than normal production time.

As in the first edition, Dr. Dubois contributes the majority of supplements, drawing on his vast personal experience in this still baffling disorder. Some chapters have been revised such as Pathology of the Kidney in Systemic Lupus Erythematosus: Serial Renal Biopsy Studies and Effects of Therapy on Kidney Lesions by Drs. Pollak and Pirani while others are reprinted intact from the first edition and then revised by two supplements.

The chapter dealing with the Clinical Picture of Systemic Lupus Erythematosus provides a comprehensive view of the many variable forms in which this disorder may appear and makes abundantly clear why SLE is the rightful heir to the great imitation crown formerly associated with syphilis. The chapter on the LE cell is probably the most detailed of any extant and should be required reading for both physicians and the laboratory technologists required to scan and rescan multiple repeated LE preparations when one would do. If any section could be described as too short it would be the final chapter on Causes of Death in SLE in which the observation that deaths due to central nervous system disease are decreasing over the past ten years may come as a surprise to some other specialists in this field.

The first edition 1453-item Bibliography has grown to 2975 and provides us with an outstanding resource. As in the first edition, the microphotographs and tabular summaries are excellent and the color plates are a tribute to Dr. Dubois' own interest in photography.

It may be the very scope and exhaustive approach of this work that will make it difficult for the general physician to find a guide to the individual case. A chapter on Principles of Diagnosis, Differential Diagnosis and Management would, I believe, make the book more valuable to those who seek guidance in this complex world between the bedside and the immunology laboratory.

This second edition does provide the rheumatologist with a fascinating view of changes produced by the last eight years of intensive clinical and laboratory research but to the non-expert the technique of the double chapter may appear wasteful and confusing. The next revision hopefully will yield a fusion of the old and the new.

WALLACE V. EPSTEIN, MD

* * *

PRINCIPLES OF DRUG ACTION: The Basis of Pharmacology—Second Edition—Avram Goldstein, MD, Lewis Aronow, PhD, and Sumner M. Kalman, MD, Professors of Pharmacology, Stanford University School of Medicine, Stanford, California. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 854 pages, $21.50.

When a physician writes a prescription he quite properly is thinking about the actions of the drugs contained in his prescription, on organs, organ systems or patho-physiological states. Most textbooks of pharmacology are oriented to the practitioner's need for this type of information. However, this book looks at the drug action from the point of view of the pharmacologist. Its pages contain an excellent summary of our present knowledge of principles of drug action. The authors utilize drugs of different types to illustrate a particular principle and the reader is forced to the realization that many drug groups and poisons have more in common than therapeutic or toxic actions would indicate.

Fourteen chapters of this second edition are entitled "Molecular Mechanisms of Drug Action," "The Absorption, Distribution and Elimination of Drugs," "Drug Metabolism," "The Time Course of Drug Action," "Drug Toxicity," "Pharmacogenetic and Drug Idiosyncrasy," "Drug Allergy," "Drug Resistance," "Drug Tolerance and Physical Dependence," "Chemical Mutogenesis," "Chemical Carcinogenesis," "Chemical Teratogenesis," "Drug Development," and "Drug Evaluation in Man."

This should be a required text for all students of the health sciences but because of the many demands on the students' time, it will usually be read only by students with a primary interest in pharmacology. Nevertheless, it should be in the library of every practitioner who deals with drugs and patients on a daily basis. It contains the answers to many questions which arise in the daily practice of medicine and is actually a remarkable condensation and interpretation of an exploding literature on the fundamentals of pharmacology and toxicology. Fortunately, basic principles change slowly; this book will have double or triple the useful life of a standard systematic textbook of pharmacology. In addition to being an essential text for all students of pharmacology and a highly recommended reference for all medical students and practitioners of drug therapy, it is also a useful basic reference for scientists other than pharmacologists who wish to incorporate drugs or chemicals into their research programs. The book is well illustrated and referenced and the style is enticing. It can be read with pleasure and profit by novice and experienced pharmacologists alike.

H. W. Elliott, MD

* * *

IMMUNOLOGICAL ASPECTS OF SKIN DISEASES—Edited by Lionel Fry, BSc, MD, MRCP, and P. P. Seah, MB, MRCP, Department of Dermatology, St. Mary's Hospital, London. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York City (10016), 1974. 289 pages, $19.95.

This is a slim volume by a number of internationally known authors covering six dermatological problems, dermatitis herpetiformis (DH), pemphigus and pemphigoid, lupus erythematosus, malignant melanoma, vasculitis, and eczema. The chapter on dermatitis herpetiformis is written by the British editors, Drs. Fry and Seah. It is a concise and lucid account of the present standing of this disease. Although there is still some dispute as to the diagnostic criteria for DH notably by Drs. Shuster and Marks, the authors maintain that the presence of IgA deposits on the reticulin fibers of the dermal papillae and upper dermis in the uninvolved skin is necessary for the diagnosis. If this is accepted then the authors show that the disease is associated with a 95 percent incidence of gluten sensitive enteropathy. (Multiple biopsies may be necessary to establish the gut abnormality and this may not be evident macroscopically but only microscopically by counting the number of intraepithelial lymphocytes, which are high in the disease.) DH may be controlled by a strict gluten-free diet alone although this may take months, even years, of diet before dapsone can be completely discontinued. They believe that celiac disease and DH are essentially manifestations of the same disease process, the significant difference being the presence of the IgA deposits in DH and not in celiac disease. Antireticulin antibodies have been found in both diseases and it may be that in DH both the reticulin in the skin and gut is abnormal but only in the gut in celiac disease. Immune complexes are found in DH and celiac disease and C3 deposits without Clq are found in the skin in DH. They suggest that the immune complexes, where gluten is the immunogen, react with IgA deposits in the skin fixing complement by the alternate pathway which is followed by the formation of membrane vacuoles (which they have demonstrated at the ultrastructural level) which appear to enlarge to form the blister characteristic of DH.

Taking this chapter as a model for the rest of the book, a happy balance of information for the dermatologist, internist and immunologist alike, in that historical, clinical and pathological features, immunological techniques and findings, therapy and conclusions are discussed, certain chapters seem uneven. Thus, the discussion of pemphigus and pemphigoid where great advances have been made in the finding of both circulating and *in vivo* bound antibody to the intercellular cement substance in pemphigus and to the basement membrane in pemphigoid, covers mainly the principles and methodology in immunofluorescence. This is unfortunately discussed again in a subsequent chapter. Only a few pages are devoted to the diseases, which though familiar to the dermatologist are not so for other specialists, and no mention is made of clinical features or therapy.

There is only one page of references whereas by contrast Professor Stephanie Jablonska gives thirty pages which though admirable might be a little extreme in such a short book. However, her chapter is excellent and comprehensive. Of particular note for the clinician, the investigation of lupus is not complete without tests for anti-DNA antibodies, serum complement levels and skin immunofluorescence. The latter is positive in normal skin, preferably taken from the dorsum of the wrist, in SLE but negative in discoid LE but may be positive in the active disease in both. The patterns of ANA staining are clearly discussed and their relation to the diagnosis of drug induced and spontaneously occurring collagen diseases.

In the chapter on vasculitis there is an excellent review of the experimental work in animals on the Arthus, Shwartzman and serum sickness reactions but their relations to the clinical state are summarily dealt with.

Professor Nairn discusses the immunogenic nature of malignant melanoma. He includes a great deal of detail concerning laboratory techniques which might seem unnecessary. Although cell mediated immunity is probably most important locally, serum cytotoxic antibodies against melanoma cells are demonstrable in primary disease but tend to disappear with dissemination suggesting that they are of value in preventing blood-borne metastasis. Their possible role in and the concept and possibilities of immunotherapy are discussed.

The final chapter on eczema is logical, tracing the discovery of the P-K serum factor to the isolation of the reaginic antibody IgE. The relevance of increased levels of circulating IgE to atopic eczema, a disease characterized histologically by the presence of lymphocytes more reminiscent of a delayed hypersensitivity reaction is discussed. The current hypothesis is that the disease is a result of a malfunctioning immunological mechanism which may result from excessive antigen stimulation of a normally responsive IgE system during a transient gut IgA deficient period in infancy. The section on contact dermatitis will be familiar to most readers.

In summary, this is a good book, short and inexpensive providing a lot of very useful information. It might however be improved if it were better balanced.

Anthony du Vivier, MB, MRCP

cma

PROGRAM

CALIFORNIA MEDICAL ASSOCIATION

105th Annual Session and 5th Western Scientific Assembly

February 6-11, 1976

Hyatt Regency
and
Sheraton-Palace
San Francisco

- Scientific-Educational Programs
- Scientific and Technical Exhibits
- Meetings of the House of Delegates
- Woman's Auxiliary Convention

Contents

Special Conferences

American College of Physicians 4, 7

The Medical Profession and Sexuality: An Essential Dimension in Patient Care 4

Pediatric Venereology and Sexuality Sexuality, Venereal Diseases and Drug Use ... 5

Judicial, Legal and Medical Liaisons 6

Cancer of the GI Tract: The Gut Issues 8

Tumors of the Thyroid 8

Treating Alcoholism and Other Drug Abuse 9

A Conference on Death and Dying How to Avoid a "Cop Out" 9

Clinical Pharmacology for the Practitioner 12

Specialty Sections

Allergy 10

Chest Diseases 3

Dermatology 10

General and Family Practice 6

General Surgery 8

Industrial Medicine and Surgery 3

Internal Medicine 4, 7

Neurology 3, 5

Nuclear Medicine 7

Obstetrics and Gynecology 10

Ophthalmology 11

Orthopedics 8

Otolaryngology 6

Pathology 7

Pediatrics 5, 6

Physical Medicine and Rehabilitation 3, 5

Plastic Surgery 8, 11, 12

Preventive Medicine and Public Health 13

Psychiatry 6, 9

Radiology 4, 7

Urology 12

The Board Room Series 13

Preregistration Forms 14

House of Delegates Tentative Agenda 15

Proposed CMA Constitutional Amendments 16

Information

PLEASE NOTE

All meeting room assignments, not available at press time, will appear in the Annual Session Handprogram.

BADGES

It is important that badges be worn at all times. Admission to all meetings and exhibits is by badge only.

REGISTRATION

Registration will take place in the Hyatt Regency Hotel, starting Friday, February 6 through Monday, February 9, 9:00 am to 5:00 pm.

All members, guests and visitors are requested to register immediately on arrival.

Admission to the conferences and section meetings, as well as to the exhibit area, is by badge only.

Members wishing to vote in specialty sections must indicate the appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION

All MDs with credentials showing that they hold a valid license to practice medicine (e.g., membership card in CMA, AMA or county medical society).

Medical students upon presentation of credentials from their medical schools, letters from dean's office, or membership card in CMA, AMA or AMSA.

Medical assistants upon presentation of letter from a physician-employer or AAMA membership card.

Military paramedical personnel upon presentation of a letter from their commanding officer.

Dentists (DDS); Doctors of Veterinary Medicine (DVM); registered nurses (RN); student nurses, x-ray technicians; allied public health personnel and others will be admitted provided they have proper identication.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

SHUTTLE BUS

There will be shuttle bus service between the Hyatt Regency and the Sheraton-Palace Hotels during the hours when meetings are in progress.

Plan to Visit the Exhibits

Hyatt Regency Hotel

9:00 a.m. to 5:00 p.m.

FRIDAY-MONDAY

FRIDAY, FEBRUARY 6

SECTIONS ON NEUROLOGY AND PHYSICAL MEDICINE AND REHABILITATION
and
DEPARTMENTS OF NEUROLOGY AND PHYSICAL MEDICINE AND REHABILITATION
UNIVERSITY OF CALIFORNIA, DAVIS, SCHOOL OF MEDICINE
present

Neurological Problems of the School Age Child

$40 registration fee—program limited to 100 registrants (includes lunch each day)

Please use preregistration form on page 14

Program Planners:
Harold M. Sterling MD, Davis
Pierre M. Dreyfus, MD, Davis

Moderator: Pierre M. Dreyfus, MD, Davis

Panelists:
Bruce Berg, MD, San Francisco
Barbara K. Keogh, PhD, Los Angeles
David Leaverton, MD, Davis
Nicholas Lenn, MD, Davis

9:00 **Learning Disabilities**

10:10 Coffee break

10:30 **Unusual Seizures**

11:15 **Hyperactivity**

12:00 **Neurology Section Business Meeting**
Chairman: James R. Nelson, MD, La Jolla
Secretary: Pierre M. Dreyfus, MD, Davis
Assistant Secretary: Howard Siedler, MD, Kentfield

Physical Medicine and Rehabilitation Section Business Meeting
Chairman: Walter Treanor, MD, San Francisco
Secretary: William LaJoie, MD, Palos Verdes
Assistant Secretary: Harold M. Sterling, MD, Davis

12:30 **Luncheon Discussion Groups with Program Participants**

Early Intervention in Neuromuscular Disorders

Cosponsored by
Department of Physical Medicine and Rehabilitation
University of Calfornia, Davis, School of Medicine
and
California Society of Physical Medicine and Rehabilitation

Moderator: Kenneth Dumars, MD

2:00 Ulrich Aebi, MD, Berne, Switzerland

2:45 Margaret Jones, MD, Los Angeles

3:30 Break

3:45 Miriam Lowry, OTR, Kentfield

4:30 **Questions and Answers**

Acceptable for Category I Credit in the CMA Certification Program

Program continued on Saturday, see page 5

FRIDAY, FEBRUARY 6

Environmental and Occupational Impact on the Lung

Sponsored by
Section on Chest Diseases and
Section on Industrial Medicine

Program Planners:
Stanley Rokaw, MD, Los Angeles
Austin Givens, MD, Antioch

Moderator: Stanley Rokaw, MD, Los Angeles

9:00 **Patterns of Lung Exposure**
Uptake: Physics of Gas and Particle Movement
Deposition and Transfer: Areas of Impact, Response of Airways, Cells and Circulations
Physiologic Responses and Adaptations: Secretions, Distribution Balance, Lung Mechanics, Infection Control

9:45 **Sources for Lung Exposure**
Personal Sources: Cigarettes, Aerosols
Environmental Sources: Community Mixtures
Occupational Sources: Asbestos, Petrochemicals, Vinyls, etc.

10:30 Coffee Break

10:45 **Neoplastic Disease**—Diagnostic Armamentarium, Current and Future Management

11:30 **Obstructive Lung Disease**—Pathophysiologic Development and Diagnostic Approaches

12:15 **Industrial Medicine Section Business Meeting**
Chairman: Edward J. O'Neill, MD, Woodland Hills
Secretary: Austin E. Givens, MD, Antioch
Assistant Secretary: James M. Dobbins, MD, Santa Monica

12:30 Lunch break

Moderator: Austin E. Givens, MD, Antioch

1:45 **Infiltrative Lung Disease** — Pathophysiologic Development and Diagnostic Approaches

2:30 **Panel Discussion**
Management of the "Recipient"
How to Evaluate Functional Impairment
How to Measure Stresses of Protection Systems
How to Attribute Cause in Impaired Subjects
How to Salvage, Protect and Rehabilitate the Recipient
The Obligation to Protect in the Community and on the Job
Represented on the Panel will be a Physician, Hygienist, Physiologist, Therapist, and Legal/Political Resource Persons

3:45 **Demonstration**
Survey of Work Place
Surveillance for Physiologic Effects
Rehabilitation Techniques

4:45 **Chest Diseases Section Business Meeting**
Chairman: Wilber Hallett, MD, Burbank
Secretary: Hurley L. Motley, MD, Los Angeles
Assistant Secretary: Stanley Rokaw, MD, Los Angeles

FRIDAY, FEBRUARY 6
Sheraton-Palace Hotel

Regional Meeting of the American College of Physicians

Sponsored by
American College of Physicians, Northern California Region
Cosponsored by
Sections on Internal Medicine and Radiology

$30 registration fee
Please use preregistration form on page 7

12:00 **Registration**

1:50 **Governor's Welcome**
Maurice Fox, MD, FACP, Palo Alto

2:00 **Advances in Psychological Medicine**

Biofeedback in Migraine and Myofascial Pain
Michael Grotjahn, MD, San Francisco

Behavioral Modification in Cardiovascular Risk Reduction and Chronic Disease Rehabilitation
Allen J. Enelow, MD, FACP, San Francisco

2:50 **Questions and Answers**

3:00 Coffee break

3:30 **Controversies in Therapeutics**
Moderator: Charles E. Becker, MD, FACP, *San Francisco*

Oral Hypoglycemics
Protagonist: Peter H. Forsham, MD, FACP, San Francisco
Antagonist: Marvin D. Siperstein, MD, PhD, San Francisco

Propranolol
Protagonist: Edwin L. Alderman, MD, Stanford
Antagonist: Howard F. Morrelli, MD, FACP, San Francisco

4:30 **Questions and Answers**

5:15 **Internal Medicine Section Business Meeting**
Chairman: Walter P. Martin, MD, Carson
Secretary: Daniel W. Black, MD, Castro Valley
Assistant Secretary: Ernest Pund, MD, La Jolla

Program continued on Saturday, see page 7

FRIDAY, FEBRUARY 6

New Concepts in Shock and Trauma

Sponsored by
Extended Programs in Medical Education
University of California, San Francisco
and
CMA Committee on Scientific Assemblies

Program Planner and Moderator:
Donald Trunkey, MD, San Francisco

1:30 **Head Injury**
Julien Hoff, MD, San Francisco

2:00 **Orthopedic Injuries**
Michael Chapman, MD, San Francisco

2:30 **New Concepts in Shock**
Donald Trunkey, MD, San Francisco

3:00 Coffee Break

3:15 **Multiple Organ Failure**
F. William Blaisdell, MD, San Francisco

3:45 **Transfusion in Emergencies**
George Sheldon, MD, San Francisco

4:15 **Questions and Answers**

Acceptable for Category I Credit in the CMA Certification Program

FRIDAY, FEBRUARY 6

The Medical Profession and Sexuality: An Essential Dimension in Patient Care

Sponsored by
CMA Committee on Continuing Medical Education
and
CMA Task Force on Venereal Disease
in cooperation with
UC-Davis School of Medicine

Registration Fee:
(includes luncheon and reference materials)
CMA Member $60
Non-Member $90
Interns, Residents $15
Please use preregistration form on page 14

9:00 **Welcome and a Brief Introduction to the Course and Faculty**
Neil C. Andrews, MD, Davis

9:15 **Sex and the Medical Profession** (a film)

9:40 **Sex Confronts the Adolescent—Their Problems and Ours**
Gordon D. Jensen, MD, Davis

10:10 **Sexual Response—Perfect, less than perfect, dysfunctional?**
Mina M. Robbins, PhD, Sacramento

10:40 Coffee Service

11:00 **How to do it in Ten Minutes—Identification, Diagnosis, Management of Your Patient's Sexual Problems**
Jack Annon, PhD, Honolulu

12:00 **Sexuality in Old Age**
Alex Comfort, MB, PhD, Santa Barbara

1:30 **Sex Therapy** (selected films)

2:30 **You've Got What?—An update on the current treatment of sexually transmitted diseases of the New Morality**
Ellis N. Mitchell, MD, San Francisco

3:30 **Every Man Does, Every Woman Can—The treatment of preorgasmic women**
Mina M. Robbins, PhD, Sacramento

4:00 **Variations on the Theme—A pathway to understanding patients with sexual preferences different from yours**
Ian D. Barlow, MD, San Francisco

5:00 Reception

6:00 **Taking the Worry out of Being Close—The physician's role and responsibility in birth control counseling**
Felicia Stewart, MD, Sacramento

6:30 **Management of Special Problems—Medical, surgical, and deforming or disabling conditions, and their impact on sexuality**
Mina M. Robbins, PhD, Sacramento

7:00 **Open Forum**
Moderator: Neil C. Andrews, MD
Panel:
Drs. Annon, Barlow, Comfort, Jensen, Mitchell, Robbins, and Stewart
Adjournment of Conference

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

SECTIONS ON NEUROLOGY AND PHYSICAL MEDICINE AND REHABILITATION
and
DEPARTMENTS OF NEUROLOGY AND PHYSICAL MEDICINE AND REHABILITATION
UNIVERSITY OF CALIFORNIA, DAVIS
SCHOOL OF MEDICINE
present

Rheumatoid Disease in Childhood

Moderator: Walter Treanor, MD, San Francisco

9:00 Robert Swezey, MD, Los Angeles

9:45 Virgil Hanson, MD, Los Angeles

10:30 Coffee break

10:45 George Lockie, MD, San Diego

11:30 **Questions and Answers**

12:00 **Luncheon discussion groups with program participants**

Myelomeningocele

Moderator: Harold M. Sterling, MD, Davis

1:30 John Eisele, MD, San Diego

2:00 Tom Gucker, MD, Los Angeles

2:30 **Questions and Answers**
Panel: Drs. Eisele, Gucker, Aebi

3:00 Break

3:15 Richards Lyon, MD, Berkeley

3:45 Daniel Merrill, MD, Martinez

4:15 **Questions and Answers**
Drs. Lyon and Merrill

5:00 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

Pediatric Venereology and Sexuality

Sponsored by
Venereal Disease Task Force
CMA Committee on Alcoholism and Other Drug Dependence
Section on Pediatrics

$15 registration fee.

Please use preregistration form on page 14

Program Planners:
David D. Sachs, MD, San Francisco
Arthur Bolter, MD, San Leandro
Nord Nation, MD, Los Angeles

Moderator: David D. Sachs, MD

9:00 **Congenital Syphilis**
Victor Newcomer, MD, Santa Monica

Conjunctivitis of the Newborn and Related Entities
H. Bruce Ostler, MD, San Francisco

Other Sexually Transmitted Diseases
Stephan Billstein, MD, Sacramento

Questions and Answers

10:30 Break

10:45 **Legal Status of Adolescents**
William B. Sturgeon, JD, San Francisco

Adolescent Gynecology
Robert A. Sack, MD, Whittier

Questions and Answers

Sexuality, Venereal Diseases and Drug Use

12:00 **Luncheon Discussion Groups with Program Participants**
(Registrants will select a topic when they preregister.)

Syphilology
Victor Newcomer, MD

Oculogenital Syndromes
H. Bruce Ostler, MD

Minor Venereal Diseases
Stephan Billstein, MD

Legal Status and Adolescents
William B. Sturgeon, JD

Sexuality in Teenagers
Robert A. Sack, MD

Sexuality and Motherhood in Drug Abusing Women
Josette Mondonarro, MD

Serologic Tests for Syphilis
Denny L. Tuffanelli, MD

Hepatitis
Martin Goldfield, MD

Genetic Counseling for the Adolescent
Allan J. Ebbin, MD

Thyroid Disease in Adolescents
Ann K. Kershnar, MD

Adolescents and Sports
Frank W. Jobe, MD

Surgical Management of Thyrotoxicosis in Children
Jordan J. Weitzman, MD

Moderator: Arthur Bolter, MD, San Leandro

2:30 **Serologic Tests for Syphilis in Narcotic Users**
Denny L. Tuffanelli, MD, San Francisco

3:00 **Hepatitis B Virus as a Sexually Transmitted Disease**
Martin Goldfield, MD, Trenton, New Jersey
Assistant Commissioner, New Jersey Department of Health

Questions and Answers

4:00 Break

4:10 **Women's Sexual Desires and Abilities with Drug Use**
Josette Mondonarro, MD, San Francisco

Questions and Answers

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

Adolescent Medicine

Sponsored by
Section on Pediatrics
Cosponsored by
American Academy of Pediatrics, District 9

Moderator and Program Planner:
Nord Nation, MD, Los Angeles

12:00 **Luncheon Discussion Groups with Program Participants**
Please use preregistration form on page 14

2:00 **Genetic Counseling to the Adolescent**
Allan J. Ebbin, MD, Los Angeles
Questions and Answers

2:45 **Diagnosis and Treatment of Thyroid Disease in Adolescents**
Ann K. Kershnar, MD, Tustin
Questions and Answers

3:30 Break

3:45 **Surgical Management of Thyrotoxicosis in Children**
Jordan J. Weitzman, MD, Los Angeles
Questions and Answers

4:30 **Adolescents and Sports**
Frank W. Jobe, MD, Los Angeles
Orthopedic Consultant for the Los Angeles Dodgers
Questions and Answers

5:15 **Pediatric Section Business Meeting**
Chairman: Nord Nation, MD, Los Angeles
Secretary: Edward J. Ottenheimer, MD, San Diego
Assistant Secretary: Pat Henderson, MD, Fresno

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

Ear, Nose and Throat Problems in Children

Sponsored by
Sections on General and Family Practice and Otolaryngology
Cosponsored by
Extended Programs in Medical Education
University of California, San Francisco

Program Planners:
Sam W. Smith, MD, Lemon Grove
Roger Boles, MD, San Francisco
Moderator: Herbert H. Dedo, MD, San Francisco

Panel Discussions:
8:30 **Croup and Epiglottitis: Recent Developments and Therapy**
Moderator: Roger Crumley, MD, San Francisco

9:30 **Hearing Problems: Modern Techniques of Evaluation and Habilitation**
Moderator: Mansfield F. W. Smith, MD, San Jose

10:30 Coffee Break

11:00 **Otitis Media: Current Concepts of Diagnosis and Treatment**
Moderator: Leslie Bernstein, MD, DDS, Davis

12:00 Lunch Break

1:30 **Otolaryngology Section Business Meeting**
Chairman: Mansfield F. W. Smith, MD, San Jose
Secretary: Robert Kohut, MD, Irvine
Assistant Secretary: Roger Boles, MD, San Francisco

General and Family Practice Section Business Meeting
Chairman: Nicholas P. Krikes, MD, San Bernardino
Secretary: John Bridgeman, MD, Mission Viejo
Assistant Secretary: Sam W. Smith, MD, Lemon Grove

2:00 Workshops
Each will last 30 minutes and will be repeated four times, so that participants may attend all four.

Nose Bleeds: Practical Methods of Management
Leader: Tom Miller, MD, Oakland

Evaluation of Hearing in Infants and Children: Modern Techniques
Leader: Robert A. Schindler, MD, San Francisco

T & A, Myringotomy and Tympanostomy Tubes: How to Do It
Leader: Philip C. Bartlett, MD, San Francisco

Laryngoscopy, Tracheal Intubation and Tracheostomy in Infants and Children: Practical Management of Airway Problems
Leader: Willard E. Fee, MD, Stanford

4:00 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

Judicial, Legal and Medical Liaisons

Sponsored by
Section on Psychiatry
CMA Committee on Mental Health

Program Planners:
Melvin M. Lipsett, MD, Berkeley
Stanley Bergreen, MD, Downey
Stuart L. Brown, MD, San Diego

Moderator: Stanley Bergreen, MD, Downey
Speakers to be announced

9:00 **Keynote Address**

Panel Discussion
9:45 **Lanterman-Petris-Short Act: Current Problems in Its Implementation**

10:45 Break

11:00 **Conservatorship**

11:45 Lunch Break

1:45 **Psychiatric Problems Relating to a Juvenile Homicide**

2:30 **Advocacy for Children in the Courts**

3:15 Break

3:30 **Confidentiality of Records**

4:15 **Prearraignment and Criminal Responsibility**

5:00 **Panel Discussion**
Medical Liability

SATURDAY, FEBRUARY 7

Sheraton-Palace Hotel

Regional Meeting of the American College of Physicians

Sponsored by
American College of Physicians, Northern California Region
Cosponsored by
Sections on Internal Medicine and Radiology

$30 registration fee
Please use preregistration form below

8:15 **Radiology Section Business Meeting**
Chairman: Fred K. Sondheimer, MD, San Francisco
Secretary: William Pogue, MD, San Diego
Assistant Secretary: Peter Kane, MD, Oakland

8:30 **Abdominal Disease: Advances in Diagnosis and Management**
Moderator: Martin Brotman, MD, FACP, San Francisco

Gastrointestinal Hemorrhage: Diagnostic and Therapeutic Angiography
Josef Rosch, MD, Professor of Radiology
University of Oregon Medical School

New Trends in Diagnosis of Pancreatic and Biliary Lesions

Ultrasonography
George Leopold, MD, San Diego

Angiography
Helen C. Redman, MD, San Francisco

Endoscopic Retrograde Cholangiopancreatography
Joseph P. Belber, MD, FACP, Davis

Body Scanning
Ralph J. Alfidi, MD, Director of Diagnostic Radiology
Cleveland Clinic Hospital

Questions and Answers

10:10 Coffee

10:30 **Vitamin D: Metabolic and Clinical Aspects**
Charles Kleeman, MD, FACP, Los Angeles

11:30 **Presentation by Representative of the American College of Physicians**

12:00 **Luncheon: "Meet the Professor" Discussions**

1:45 **Physiology and Clinical Implications of Hypothalamic Hormones**
Moderator: Daniel D. Federman, MD, FACP, Stanford

Gonadotropin Release Hormone
Melvin M. Grumbach, MD, San Francisco

Somatostatin
John E. Gerich, MD, San Francisco

3:00 Coffee Break

3:30 **Clinical Relevance of Studies on the Lymphocyte**

Physiology of the Lymphocyte
Speaker to be announced

Clinical Applications
Norman Talal, MD, San Francisco

4:20 **Questions and Answers**

4:40 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

SATURDAY, FEBRUARY 7

Everything You Always Wanted to Know About a Thyroid Nodule but Were Afraid to Ask

Sponsored by
Sections on Nuclear Medicine and Pathology
Cosponsored by
California Society of Pathology
Northern California Chapter of The Society of Nuclear Medicine
Southern California Chapter of The Society of Nuclear Medicine
Sierra Valley Nuclear Medicine Association

Program Planners:
Emmett Reilly, MD, Inglewood
Richard C. Ripple, MD, Sacramento
Moderator: Jan K. Siemsen, MD, Los Angeles

8:45 **Diagnostic Studies of Nodules in the Thyroid**
Paul B. Hoffer, MD, San Francisco

9:30 **An Internist Discusses the Thyroid Nodule**
Francis S. Greenspan, MD, San Francisco

10:15 Break

10:30 **A Surgeon Discusses the Thyroid Nodule**
George Crile, Jr., MD, Cleveland

11:15 **Panel Discussion of Patients Presenting with Nodular Thyroids**
Moderator: William H. Blahd, MD, Los Angeles
William A. Meissner, MD, Boston
George Crile, Jr., MD, Cleveland
Francis S. Greenspan, MD, San Francisco
Paul B. Hoffer, MD, San Francisco

12:15 **Nuclear Medicine Section Business Meeting**
Chairman: John R. White, MD, Torrance
Secretary: Richard C. Ripple, MD, Sacramento
Assistant Secretary: Jorge Franco, MD, San Jose

Pathology Section Business Meeting
Chairman: Stebbins Chandor, MD, Los Angeles
Secretary: Joseph H. Masters, MD, Sacramento
Assistant Secretary: Emmett Reilly, MD, Inglewood

Acceptable for Category I Credit in the CMA Certification Program

---

American College of Physicians

FRIDAY, FEBRUARY 6
SATURDAY, FEBRUARY 7

$30 registration fee
Sheraton-Palace Hotel

Name _____

Address _____

City _____ Zip _____

Please make check payable to the American College of Physicians.

Return this application with total remittance to:

LINDA CLEVER, MD
St. Mary's Clinic
2235 Hayes Street
San Francisco, CA 94117

SATURDAY, FEBRUARY 7

Terrace Room—Fairmont Hotel

Cancer of the GI Tract: The Gut Issues

Sponsored by
American Cancer Society, California Division
CMA Section on General Surgery

Cosponsored by
CMA Committee on Cancer

Moderators and Program Planners:
Robert J. Schweitzer, MD, Oakland
Harry A. Oberhelman, Jr., MD, Stanford

1:00 **Welcome**
Robert J. Schweitzer, MD, Oakland

1:05 **Current Aspects of Endoscopy and Diagnosis of GI Malignancies**
Harvey W. Olsen, MD, Oakland

1:45 **The Role of Radiation Therapy**
Philip Rubin, MD, Rochester, New York
Professor and Chairman, Division of Radiation Oncology, University of Rochester

2:25 **Surgical Treatment of Colon-rectal Cancer**
Maus W. Stearns, Jr., MD, New York City
Chief, Colon-Rectal Service, Memorial Hospital

3:05 **The Role of Chemotherapy**
Charles G. Moertel, MD, Rochester, Minnesota
Professor, Mayo Graduate Medical School

3:45 **Panel Discussion**
Controversies in Management
Moderator: Robert J. Schweitzer, MD, Oakland

4:45 Discussion Period

5:00 **General Surgery Section Business Meeting**
Chairman: Earl F. Wolfman, Jr., MD, Davis
Secretary: Fred Turrill, MD, Glendale
Assistant Secretary: Harry A. Oberhelman, Jr., MD, Stanford
Adjournment

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 8

Principles of Plastic Surgical Wound Closure

Sponsored by
Section on Plastic Surgery

Cosponsored by
The California Society of Plastic Surgeons

A workshop on suturing techniques for the family practitioner, general surgeon or emergency room physician. This course will stress those techniques which might be useful under emergency room conditions.

$45 Registration fee for laboratory. Enrollment limited to 50 participants.

2:00-4:00 p.m. **Laboratory**
Faculty: Roger P. Friedenthal, MD, and staff.

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 8

Terrace Room—Fairmont Hotel

SEMI-ANNUAL SEMINAR OF THE
CALIFORNIA TUMOR TISSUE REGISTRY

Tumors of the Thyroid

9:00 to 4:30 This seminar is primarily intended for the continuing education of pathologists. Any physician interested in the pathology of thyroid disease is welcome to attend.

Registration information:
$100 fee includes a set of 25 microscopic slides and clinical histories which will be mailed in advance to registrants. A syllabus will be distributed after the seminar.

$50 fee includes attendance at the seminar and the syllabus.

No fee to Residents or Interns for attendance only.

Moderator:
William A. Meissner, MD
Clinical Professor of Pathology
Harvard Medical School
New England Deaconess Hospital
Boston, Massachusetts

For information contact:
The California Tumor Tissue Registry
1200 N. State Street, Box 40
Los Angeles, California 90033

SUNDAY, FEBRUARY 8

Competitive Sports and Athletic Injuries

Sponsored by
Section on Orthopaedics

Moderator and Program Planner:
Sonny Cobble, MD, Los Angeles

9:00 **Injuries of the Cervical Spine**
Stephen Pye, MD, San Diego
Richard Braun, MD, San Diego

9:30 **Injuries of the Lumbar Spine**
Douglas Jackson, MD, Long Beach

10:00 **Emergency Care of the Injured Athlete**
Philip McFarlane, MD, Fullerton

10:30 Break

10:45 **Arthroscopy of the Knee**
Richard O'Connor, MD, West Covina

11:15 **Arthrography of the Knee**
Richard Wolff, MD, San Francisco

11:45 **Rehabilitation Following Knee Injuries**
John Fagin, MD, San Francisco

12:15 **Ankle Injuries**
James Glick, MD, San Francisco

12:45 **Orthopaedic Section Business Meeting**
Chairman: Sonny Cobble, MD, Los Angeles
Secretary: Ben Colloff, MD, San Francisco
Assistant Secretary: F. Bruce Kimball, MD, La Jolla
Adjournment

SUNDAY, FEBRUARY 8

Treating Alcoholism and Other Drug Abuse

Sponsored by
California Society for the Treatment of Alcoholism and Other Drug Dependencies

Cosponsored by
CMA Committee on Alcoholism and Other Drug Dependence
American Medical Society on Alcoholism

Registration Fee: $20
Please use preregistration form on page 14

Moderator and Program Planner:
Vernelle Fox, MD, Long Beach

8:30 **Registration**

9:00 **Management of Mixed Dependency—Alcohol and the "Soft Drugs"**
Vernelle Fox, MD, Long Beach

9:45 **Treatment Techniques for the Polydrug Abuser: Including Drug Maintenance and Biofeedback**
Donald R. Wesson, MD, San Francisco

10:30 Break

10:45 **New Psychopharmacological and Biochemical Research: Indications for the Future**
Kenneth Blum, PhD, Chief
Division of Drug and Alcohol Abuse, University of Texas

11:15 **Questions and Answers**

12:00 **Luncheon Discussion Groups with Program Participants**
Registrants will select a topic when they preregister.

- **Mixed Addictions Involving Alcohol—Detoxification and Recovery**
- **Street Drugs (information from street drug analysis programs, physiologic reactions to today's street drugs, etc.)**
- **Current Trends in Alcohol Research**
- **New Pharmacology in the Treatment of Heroin Addiction**
- **Postgraduate Physician Education about Chemical Dependencies**
- **The Recovery Process from Alcoholism**
- **The Recovery Process from Barbiturate or Opiate Dependencies**
- **Special Case Presentation and Discussion Using Slide-sound Media**

1:45 **Special Problems of Women Alcoholics**
Florette Pomeroy, San Francisco
Questions and Answers

2:30 **Approaches to Chemically Dependent Patients: How Attitudes of the Physician Influence Treatment**
John Chappel, MD, Career Teacher,
University of Nevada, Reno
Questions and Answers

3:15 Break

3:30 **Business Meeting of the California Society for the Treatment of Alcoholism and Other Drug Dependencies**
President: Charles E. Becker, MD, San Francisco
Vice-President: Vernelle Fox, MD, Long Beach
Secretary-Treasurer: Arthur Bolter, MD, San Leandro

5:00 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 8

Current Issues in Psychiatry A Discussion in the Round

Sponsored by
Section on Psychiatry

Cosponsored by
Southern California Psychiatric Society

Moderator and Program Planner:
William Holyoak, MD, Beverly Hills

9:00 **Misconceptions About Anxiety**
Dominic F. Rendinell, MD, Los Angeles
Stress and Adaptation
Mardi Horowitz, MD, San Francisco
Psychotherapy and the Coronary Patient
Charles W. Wahl, MD, Los Angeles
Adolescents and Family Marital Conflicts
Marjorie Hayes, MD, San Francisco
Rape! Who Cares
Martha J. Kirkpatrick, MD, Los Angeles
ECT Controversy
Howard Gurevitz, MD, Hillsborough

12:00 **Psychiatry Section Business Meeting**
Chairman: George A. Gross, MD, Sacramento
Secretary: William Holyoak, MD, Beverly Hills
Assistant Secretary: Robert Solow, MD, Beverly Hills

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 8

A Conference on Death and Dying How to Avoid a "Cop Out"

Sponsored by
CMA Committee on Medicine and Religion

Program Planner: Albert E. Long, MD, San Francisco
Moderator: A. Norton Donaldson, MD, Santa Ana

2:30 **Panel Discussion**

Deanna M. Dimmitt, PharmD
Director of Pharmacy
Ross General Hospital

Pat Hess, RN, MS
Assistant Professor of Nursing
San Francisco State University

Reverend Jack Humphrey
Director, Clinical Pastoral Education
Presbyterian Hospital of Pacific Medical Center

William Lamers, MD
Instructor in Psychiatry
University of California, San Francisco

4:30 **Adjournment**

SUNDAY, FEBRUARY 8

SECTION ON ALLERGY AND THE CALIFORNIA SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

present

Special Problems in Asthma

Please use preregistration form below

Moderator and Program Planner:
Arthur Turk, MD, Garden Grove

8:40 **Opening Remarks**

8:45 **Management of the Pregnant or Nursing Patient with Asthma**
Joseph L. McGerity, MD, San Francisco

9:20 **Indications for Institutionalization of a Patient with Asthma—What to Expect**
Elliott Middleton, Jr., MD
The National Asthma Center, Denver, Colorado

10:40 **Status of Newer Drugs for Asthma**
Sheldon C. Siegel, MD, Los Angeles

11:15 **Panel Discussion**
Rational Use of Corticosteroid Drugs
Drs. Middleton, Siegel, McGerity, Galant, Stevenson

12:30 Luncheon
Annual Business Meeting of the California Society of Allergy and Clinical Immunology and CMA Section on Allergy
Chairman: William Sayer, MD, Palo Alto
Secretary: Arthur Turk, MD, Garden Grove
Assistant Secretary: William Ziering, MD, Fresno

Common Problems in Allergy and Dermatology—a Joint Assessment

2:00 **Urticaria—a Dermatologist's Viewpoint**
Roger C. Cornell, MD, La Jolla

2:30 **Urticaria—an Allergist's Viewpoint**
Donald D. Stevenson, MD, La Jolla

3:10 **Atopic Dermatitis—a Dermatologist's Viewpoint**
Howard Maibach, MD, San Francisco

3:40 **Atopic Dermatitis—an Allergist's Viewpoint**
Stanley P. Galant, MD, Irvine

4:15 **Discussion Period**

4:30 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

SUNDAY, FEBRUARY 8

Skin Problems of Women

Sponsored by Sections on Dermatology and Obstetrics and Gynecology

Cosponsored by California Section, American College of Obstetrics and Gynecology

$12.50 fee for luncheon

Please use preregistration form on page 14

Moderators and Program Planners:
Faye D. Arundell, MD, Menlo Park
John J. Molitor, MD, Fullerton

9:00 **Pheromones**
Jane M. Rosenzweig, MD, San Francisco

9:25 **Autoimmune Progesterone Dermatitis**
Roland Hart, MD, Stanford

9:50 **Hormonal Control of Baldness, Acne and Hirsuitism**
Vera H. Price, MD, San Francisco

10:15 Coffee Break

10:30 **Dermatoses of Pregnancy**
Wiliam Watson, MD, Stanford

11:00 **Birth Control Pills and the Skin**
Patricia G. Engasser, MD, Redwood City

11:30 Discussion Period

11:45 **Dermatology Section Business Meeting**
Chairman: Marian Brubaker, MD, La Canada
Secretary: Faye Arundell, MD, Menlo Park
Assistant Secretary: Stanley Bierman, MD, Los Angeles

12:00 Luncheon
Guest Speaker: Warren Pearse, MD, Chicago
Medical Director, American College of Obstetrics and Gynecology

2:00 **Obstetrics and Gynecology Section Business Meeting**
Chairman: Theodore W. Loring, MD, Eureka
Secretary: John Molitor, MD, Fullerton
Assistant Secretary: Roger Miesfeld, MD, San Diego

2:30 **Impact of Federal and State Regulations on the Practice of Obstetrics and Gynecology**
Panel Discussion

3:30 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

---

Special Problems in Asthma

Common Problems in Allergy and Dermatology

$15 for luncheon reservation.

SUNDAY, FEBRUARY 8

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Section on Allergy.

Return this application with total remittance to:

WILLIAM ZIERING, MD
3760-1st
Fresno, CA 93702

SUNDAY, FEBRUARY 8

Symposium on the Cornea

Sponsored by
Section on Ophthalmology

Cosponsored by
Department of Ophthalmology, Pacific Medical Center, San Francisco

$25 registration fee.
Please use preregistration form on page 14
Moderator: Gilbert W. Cleasby, MD, San Francisco

9:00 **Corneal Physiology for the Practitioner**
George O. Waring, MD, Davis

9:30 **Herpetic Keratitis: Diagnosis and Natural History**
Phillips Thygeson, MD, Los Altos

9:50 **Herpetic Keratitis: Management**
H. Bruce Ostler, MD, San Francisco

10:10 Recess

10:30 **Herpetic Keratitis: Keratoplasty**
Max Fine, MD, San Francisco

10:55 **Trauma Management: New Developments**
Robert G. Webster, Jr., MD, San Francisco

11:20 Discussion Period

11:45 **Ophthalmology Section Business Meeting**
Chairman: Jerry Donin, MD, Pomona
Secretary: Gilbert W. Cleasby, MD, San Francisco
Assistant Secretary: George Tabor, MD, San Diego

12:00 **Lunch**

Moderator: George L. Tabor, MD, San Diego
The Executive Committee of the California Association of Ophthalmology will present brief reports

1:30 **Microsurgical Techniques and Innovations**
Steven G. Kramer, MD, San Francisco

2:00 **Ulcers and Erosions**
Thomas H. Pettit, MD, Los Angeles

2:30 **Bullous Keratopathy**
Robert L. Hetland, MD, Palo Alto

3:00 Recess

3:15 **Complications of Cataract and Vitreous Surgery**
Perry S. Binder, MD, San Diego

3:45 **Soft Contacts: Complications and Prospects**
Anthony B. Nesburn, MD, Los Angeles

4:15 **Discussion Period**

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 9

Repair of Eyelids and Orbit After Trauma

Sponsored by
Section on Plastic Surgery

Cosponsored by
California Society of Plastic Surgeons

$8.00 fee for luncheon

Please use preregistration form on page 14

Program Planners:
Richard Dakin, MD, Greenbrae
Donald A. Laub, MD, Palo Alto

Moderators:
Richard Dakin, MD, Greenbrae
John Strong, MD, Santa Ana

9:00 **Acute Injuries of the Eyelids**
Earl Rathbun, MD, Santa Rosa

9:15 **Injuries of the Globe Associated with Eyelid Injuries**
George Paris, MD, Palo Alto

9:30 **Blow-out versus Zygoma Fractures**
Raymond Kauffman, MD, San Mateo

9:45 Discussion and break

10:00 **Late Repair of Lid and Orbit**
Crowell Beard, MD, San Jose

10:15 **Post-traumatic Ptosis**
Raynold N. Berke, MD, Menlo Park

10:30 **Repair of Large Losses of the Eyelids**
Mark Gorney, MD, San Francisco

10:45 Discussion and break

11:00 **Repair of Orbital Deformities after Malunited Face Fractures**
Robert Rhoads, MD, Los Angeles

11:15 **Reconstruction of the Anophthalmic Orbit**
Lars Vistnes, MD, Palo Alto

11:30 Discussion and break

12:00 **Luncheon**
Section on Plastic Surgery Business Meeting
Chairman: Frederick M. Grazer, MD, Newport Beach
Secretary: Richard Dakin, MD, Greenbrae
Assistant Secretary: John O. Strong, MD, Santa Ana

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 9

Problems Common to Plastic and Urologic Surgery

Sponsored by
Sections on Plastic Surgery and Urology

Cosponsored by
California Society of Plastic Surgeons

Program Planners:
Richard L. Dakin, MD, Greenbrae
Donald A. Laub, MD, Palo Alto
Melvin F. Russi, MD, San Jose
Vernon Weldon, MD, Greenbrae

1:00 **Two-stage Repair of Hypospadias**
Robert Berner, MD, Palo Alto

One-stage Repair of Hypospadias
Hugh Crawford, MD, Newport Beach

What Type of Repair for the Hypospadias Patient?
Norman Hodgson, MD, Milwaukee, Wisconsin
Professor and Chairman, Department of Urology
Medical College of Wisconsin

1:45 Discussion and break

2:00 **Intersex: How the Family Practitioner Should Handle the Anxious Parents and a Plan for Determining the Appropriate Sex.**
Norman Fisk, MD, Palo Alto

Phalloplasty and Gender Reorientation
Donald A. Laub, MD, Palo Alto

Repair of Large Tissue Defects in Epispadias
John Owsley, MD, San Francisco

2:45 Discussion and break

3:00 **Repair of Post-traumatic Impotence**
Robert Loeffler, MD, Castro Valley

Newer Penile Implants for Impotence
Daniel C. Merrill, MD, Davis

Microsurgical Repair and Vasovasotomy
Sherman Silber, MD, San Francisco

3:45 Discussion and break

4:00 **Urethroplasty for Proximal Strictures**
Vernon Weldon, MD, Greenbrae

Lymphedema of the Male Genitalia
Hyzer W. Jones, MD, Oakland

4:45 Adjournment

Acceptable for Category I Credit in the CMA Certification Program

---

Spaces available for scientific and organizational exhibits

Write to:

CMA ANNUAL SESSION
731 Market Street
San Francisco, CA 94103

MONDAY, FEBRUARY 9

Topics in Urology

Sponsored by
Section on Urology

Cosponsored by
Division of Urology, Stanford

Moderator and Program Planner:
Melvin Russi, MD, San Jose

8:15 Welcome—Coffee

8:30 **Control of Recurrent Urinary Infections in the Female**
Thomas Stamey, MD, Stanford

9:00 **Urinary Tract Infections in Children**
Duncan Govan, MD, Stanford

9:20 **Questions and Answers**

9:30 **Radiation Therapy of Carcinoma of the Prostate**
Malcolm Bagshaw, MD, Stanford

9:55 **Questions and Answers**

10:00 **Operative Cure of Incontinence in the Female**
Thomas Stamey, MD, Stanford

10:30 **Surgical Correction of Urinary Incontinence in the Male**
Emil Tanagho, MD, San Francisco

11:00 **Artificial Implantable Urinary Sphincter**
Robert Kessler, MD, Stanford

11:30 **Questions and Answers**

12:00 **Urology Section Business Meeting**
Chairman: Eugene Cattolica, MD, Oakland
Secretary: J. Bernard Miller, MD, Santa Ana
Assistant Secretary: Melvin Russi, MD, San Jose

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 9

Clinical Pharmacology for the Practitioner

Sponsored by
CMA Committee on Pharmacy and Therapeutics

Cosponsored by
California Division of the American Cancer Society

Program Planner: Ronald Okun, MD, Los Angeles
Moderator: Henry W. Elliott, MD, Irvine

9:00 **Newer Antibiotics**
John Conti, MD, San Francisco

9:45 **Approach to Antiarrythmia Drugs**
William Parmley, MD, San Francisco

10:30 Break

10:45 **Progress in Cancer Quackery**
Martin Apple, PhD, San Francisco
Panel discussion on Cancer Quackery
Questions and Answers

12:00 **Adjournment**

Acceptable for Category I Credit in the CMA Certification Program

MONDAY, FEBRUARY 9

SECTION ON PREVENTIVE MEDICINE
AND PUBLIC HEALTH
CALIFORNIA ACADEMY OF PREVENTIVE MEDICINE
CALIFORNIA PUBLIC HEALTH ASSOCIATION,
NORTHERN DIVISION

present

Current Social Problems in Public Health

Cosponsored by
Department of Community Medicine
University of California, Davis, School of Medicine

Program Planner: Stephan Billstein, MD, Sacramento

Moderator: Colin T. Greenlaw, MD, Sacramento

8:00 **Legal and Preventive Medical Aspects of Complications from Mass Vaccination Programs**
H. Bruce Dull, MD
Center for Disease Control, Atlanta, Georgia

8:45 **Protection of the Agricultural Worker from Pesticide Exposure**
Jess F. Kraus, PhD, Davis
Ephraim Kahn, MD, Berkeley

9:30 Break

9:45 **Current Legislation Affecting Health of Senior Citizens**
Assemblyman John Thurman, Modesto

10:15 **Confidentiality of Records—Its Influence on Clinical and Epidemiologic Research**
George A. McKray, JD, Berkeley

11:00 **Rural Health**
Jerome Lackner, MD, Sacramento

11:45 **Preventive Medicine and Public Health Section Business Meeting**
Chairman: Colin T. Greenlaw, MD, Sacramento
Secretary: Stephan Billstein, MD, Sacramento
Assistant Secretary: Arthur C. Hollister, MD, Berkeley

12:00 Lunch Break

What Can the Physician's Assistant and Family Nurse Practitioner Do for You— In Private Medicine? In Public Health Programs?

Cosponsored by
Department of Family Practice
University of California, Davis, School of Medicine

Moderator and Program Planner:
Stephan Billstein, MD, Sacramento

1:45 **California Legislation and the Physician's Assistant and Family Nurse Practitioner**
Assemblyman Gordon Duffy, Hanford

2:30 **Role of Family Nurse Practitioner in Primary Care**
L. Hughes Andrus, MD, Davis

How to Make the Education Programs for Family Nurse Practitioners and Physicians' Assistants Responsive to Current Needs
Mary Finley, Family Nurse Practitioner, Davis

The Impact on Private Solo Practice of the Family Nurse Practitioner and the Physician's Assistant
Robert Werra, MD, Ukiah
Jean Quinones, Family Nurse Practitioner, Ukiah

Physician's Assistant vs. Family Nurse Practitioner: Differences and Similarities
Ray Kivel, MD, Los Angeles

Decentralized Education for Physicians' Assistants
Virginia Fowkes, Stanford

Discussion Period

Moderator: James Harrison, MD, Sacramento

THE BOARD ROOM SERIES

A special series of small group conferences on a variety of topics will be featured at Annual Session. Each conference will provide 15 registrants with an opportunity to question noted authorities in an informal setting. During these 90 minute sessions, breakfast, lunch, or beer and pretzels will be served.

Guests will include

William Meissner, MD
Clinical Professor of Pathology, Harvard Medical School and New England Deaconess Hospital, Boston

Norman Hodgson, MD
Clinical Professor and Chairman, Department of Urology, The Medical College of Wisconsin, Milwaukee

Josef Rosch, MD
Professor of Radiology, University of Oregon School of Medicine, Portland

William H. Blahd, MD
Chief of Nuclear Medicine, Wadsworth Veterans Administration Hospital, Los Angeles

and

Kenneth McCormack, MD
Head, Division of Nuclear Medicine, Mt. Zion Hospital and Medical Center, San Francisco

George R. Leopold, MD
Associate Professor of Radiology and Head, Diagnostic Ultrasound, University Hospital, University of California, San Diego

Preregistration information is available from California Medical Association

Preregistration Forms

Neurological Problems of the School Age Child

$40 registration fee includes two luncheons

FRIDAY, FEBRUARY 6
SATURDAY, FEBRUARY 7

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Sections on Neurology and PM&R.

Pediatric Venereology and Sexuality
Adolescent Medicine
Sexuality, Venereal Diseases and Drug Use

$15 for luncheon reservation

SATURDAY, FEBRUARY 7

Name _____

Address _____

City _____ Zip _____

1st and 2nd choices of topics for roundtable discussion:

_____

_____

Please make check payable to the CMA VD Task Force.

Principles of Plastic Surgical Wound Closure

$45 registration fee for laboratory.

(Enrollment limited to 50 participants)

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Section on Plastic Surgery.

Treating Alcoholism and Other Drug Abuse

$20 registration fee includes lunch

SUNDAY, FEBRUARY 8

Name _____

Address _____

City _____ Zip _____

1st and 2nd choices of topics for roundtable discussion:

_____

_____

Please make check payable to the California Society for the Treatment of Alcoholism and Other Drug Dependencies.

Symposium on the Cornea

$25 registration fee includes luncheon

SUNDAY, FEBRUARY 8

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Section on Ophthalmology.

Skin Problems of Women

$12.50 for luncheon reservation

SUNDAY, FEBRUARY 8

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Sections on Dermatology and Ob-Gyn.

Repair of Eyelids and Orbit After Trauma

$8 for luncheon reservation

MONDAY, FEBRUARY 9

Name _____

Address _____

City _____ Zip _____

Please make check payable to CMA Section on Plastic Surgery.

The Medical Profession and Sexuality: An Essential Dimension in Patient Care

Registration Fee:
CMA Member **$60**
Non-CMA Member **$90**
Interns, Residents **$15**
Medical Students and CMA retired members **no fee**

Fee includes lunch and reference materials

FRIDAY, FEBRUARY 6

Name _____

Address _____

City _____ Zip _____

Please make check payable to the CMA.

Return applications with total remittance to:

Department of Special Programs
California Medical Association
731 Market Street
San Francisco, CA 94103

1976 Annual Session
House of Delegates

TENTATIVE AGENDA

Sheraton-Palace Hotel, San Francisco

Joseph F. Boyle, Los Angeles ..... *Speaker*
Henry V. Eastman, Tustin ..... *Vice-Speaker*
Sanford E. Feldman, San Francisco ..... *Secretary*

SATURDAY, FEBRUARY 7, First Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:00 p.m. Sharp

1. Call to order (Invocation and Pledge of Allegiance)
2. Announcement of Reference Committees*
   - Committee on Credentials
   - Reference Committee A—Community and Environmental Health
   - Reference Committee B-1—Government Medical Programs
   - Reference Committee B-2—Government Medical Programs
   - Reference Committee C-1—Medical Economics, Insurance and Prepayment
   - Reference Committee C-2—Medical Economics, Insurance and Prepayment
   - Reference Committee D-1—Scientific and Educational Activities
   - Reference Committee D-2—Scientific and Educational Activities
   - Reference Committee E-1—Professional and Public Relations
   - Reference Committee E-2—Professional and Public Relations
   - Reference Committee F—Finance
   - Reference Committee G—Constitution and Bylaws
   - Reference Committee H—Blue Shield of California
3. Miscellaneous Announcements
4. Honored Guests
5. Report of the Committee on Credentials, and Organization of the House of Delegates—Roll Call
6. Recognition of President of Woman's Auxiliary to the CMA—Mrs. Salvadore A. Lask
7. Address by President—Carl Goetsch
8. Report of the President—Carl Goetsch
9. Report of the President-Elect—Ralph M. Milliken
10. Report of the Speaker and Vice-Speaker of the House of Delegates—Joseph F. Boyle and Henry V. Eastman
11. Report of the Trustees of the California Medical Association—Carl Goetsch
12. Report of the Physicians' Benevolence Fund, Inc.—Carl Goetsch
13. Report of the Secretary—Sanford E. Feldman
14. Report of the Editor—Malcolm S. M. Watts
15. Report of the Executive Director—Willis W. Babb
16. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber
17. Report of the Executive Committee—Carl Goetsch
18. Report of the Council—Frederick W. Ackerman, Chairman
19. Report of Blue Shield of California Trustees—Marvin J. Shapiro, Chairman
20. Reports of Commissions
21. Reports of other Committees
22. Old and unfinished business
23. New business
24. Adjournment

*Subject to revision

TUESDAY, FEBRUARY 10, Second Meeting

REGISTRATION—12:00 noon
MEETING STARTS—1:30 p.m.

(To be recessed and reconvened at 9:00 a.m., Wednesday, February 11)

1. Call to order
2. Supplemental Report of Credentials Committee—Roll Call
3. Address by President-Elect—Ralph M. Milliken
4. Introduction of President-Elect of Woman's Auxiliary to the CMA—Mrs. Harry Alton
5. Secretary's announcement of Council's selection of time and place for the 1976 Annual Session
6. Election and presentation of Officers
7. Announcement of nominations of Delegates and Alternates to the American Medical Association
8. Election of Blue Shield of California Trustees
9. Reports of Reference Committees
10. Unfinished business
11. New business
12. Adjournment

Reports of officers, commissions and committees of the California Medical Association, together with the audited financial statements for the fiscal year ended June 30, 1975, are printed in the *Annual Reports Bulletin,* which is distributed to CMA Delegates and Alternates before the meeting of the House of Delegates. The *Bulletin* is also available to any member of the Association on request directed to Executive Director, California Medical Association, 731 Market Street, San Francisco, California 94103.

PROPOSED CMA CONSTITUTIONAL AMENDMENTS

FOR ACTION IN 1976

Three Constitutional amendments were introduced in the 1975 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

The proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of *The Western Journal of Medicine* before they come before the House of Delegates for action.

CMA CONSTITUTIONAL AMENDMENT PERMITTING VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Introduced by: LACMA Delegation
Representing: Los Angeles County
Author: Allan K. Briney, MD

Constitutional Amendment No. 1-75
Committee G

Whereas, the present Bylaws of the California Medical Association make membership in the California Medical Association and the American Medical Association compulsory to all members of a component county medical society; and

Whereas, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the California Medical Association or American Medical Association; and

Whereas, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

Whereas, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privileges of setting priorities as to organizational commitments, such as belonging to specialty societies; and

Whereas, in at least forty states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations; e.g., New York and Massachusetts; and

Whereas, professional liability insurance carriers have no requirements about California Medical Association or American Medical Association membership for coverage of a county medical society member; and

Whereas, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

Whereas, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

* * *

SCIENTIFIC BOARD DELEGATES

Introduced by: ad hoc Committee on the Study of the Election Process of the Scientific Board
Representing: ad hoc Committee on the Study of the Election Process of the Scientific Board
Author: Frederick S. Armstrong, MD

Constitutional Amendment No. 2-75
Committee G

Resolved: That Article III, Part A, Section 1-d of the California Medical Association Constitution and Bylaws shall be amended by deleting the words in brackets and substituting the words in italics so that this Section shall read:

(d) [Ex-officio, without the right to vote, eighteen (18) members of the Scientific Board selected as provided in the Bylaws.] *Delegates elected by the Scientific Board.*

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

* * *

ARTICLE I, SECTION 2: NAME, PURPOSES AND ORGANIZATION

Introduced by: Henry S. Richanbach, MD
Author: William Rosenzweig, MD

Constitutional Amendment No. 3-75
Committee G

Whereas, the right of each individual to associate, or not associate freely with legally constituted organizations may not be abridged by virtue of our Constitutional rights; and

Whereas, the California Medical Association, by virtue of its mandatory requirement that the individual members and member associations affiliate themselves with the American Medical Association, it is patently clear that these rights have been, and are being abridged; now, therefore, be it

Resolved: That Article I, Section 2 of the Constitution be amended as follows:

The purposes of this Association are to promote the science and art of medicine, the protection of public health, and the betterment of the medical profession; to promote similar interests of its component societies.

ACTION: Tabled for one year; to be acted upon at the 1976 meeting of the House of Delegates.

How many of your patients know what vitamin A and vitamin C are?

But they do know what vegetables and fruits are.

The foods above have several nutrients in common. The principal ones are vitamins A and C, important for building body resistance to infection. Because citrus fruits, leafy greens, broccoli, carrots, cabbage and others provide these nutrients, these kinds of foods are classified as the Vegetable & Fruit Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

November 22—**Practical Oncology.** UCD. Saturday.

December 7—**Seminar on Head and Neck Tumors—Semi-Annual.** California Tumor Tissue Registry, Hyatt Hotel, San Francisco. Sunday. Contact: Weldon K. Bullock, MD, Exec. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

January 16-17—**Childhood Cancer: Major Clinical Advances and New Problems in Family Adjustment.** Children's Hospital of L.A. and American Cancer Society at Children's Hospital, Los Angeles. Friday-Saturday. Contact: Daniel M. Hays, MD, Children's Hospital, P.O. Box 54700, Los Angeles 90054. (213) 660-2450, ext. 2675.

January 16-18—**Gynecologic Oncology.** Women's Hospital Medical Center at Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Sunday. 15 hrs. $200; $100, residents. Contact: Margaret Frederick, Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 19-23—**Cancer.** STAN. Monday-Friday.

January 28—**Lung Cancer.** Hospital of the Good Samaritan, Los Angeles. Wednesday. Contact: Janie Sternal, Coord., CME, Hospital of the Good Samaritan, 1212 Shatto St., Los Angeles 90017. (213) 482-8111.

February 27—**Breast Cancer.** UCSF at Childrens Hospital and Medical Center, San Francisco. Friday.

MEDICINE

November 15—**Pediatric Dermatology.** Childrens Hospital of Orange County, Orange. Saturday. Contact: Merl J. Carson, MD, Med. Dir., CHOC, 1109 W. La Veta Ave., Orange 92668. (714) 633-6030.

November 15-18—**Gastroenterology: Current Topics with Emphasis on Peptic Ulcer.** UCLA at Kona Kai Hotel, San Diego. Saturday-Tuesday.

November 16—**Heparin-Thrombosis Seminar.** American Heart Assn. Council on Thrombosis; American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Sunday. $30. Contact: Symposiums International, 130 El Camino Dr., Beverly Hills 90212. (213) 273-2157.

November 16—**Hypertension.** UCLA and Granada Hills Community Hospital at Calif. State University, Northridge. Sunday.

November 17-21—**American Heart Association.** Disneyland Hotel, Anaheim. Monday-Friday. Contact: William W. Moore, Exec. V. P., AHA, 44 E. 23rd St., N.Y. 10010.

November 19-21—**Respiratory Failure.** USC. Friday-Sunday.

November 20-22—**West Coast Allergy Society.** Royal Inn at the Wharf, San Diego. Thursday-Saturday. Contact: Harvey O. Randel, MD, WCAS, 2164 SW Park Pl., Portland, Ore. 97205. (503) 226-1555.

November 22—**Nuclear Cardiology.** UCSF. Saturday.

November 22—**Management of Respiratory Failure in Infants.** See Pediatrics, November 22.

November 22—**Flexible Bronchofibroscopy.** See Surgery, November 22.

December 4-6—**Rheumatic Diseases—4th Annual Western Regional Conference.** UCSF at Claremont Hotel, Oakland. Thursday-Saturday.

December 5-6—**Diabetes Mellitus.** STAN and Santa Clara County Diabetes Assn. at Rickey's Hyatt House, Palo Alto. Friday-Saturday. Contact: STAN.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** See Of Interest To All, December 5-6.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

December 6—**Advances in Diabetes Mellitus, Calcium and Water Disorders.** Daniel Freeman Memorial Hospital at International Hotel, Los Angeles. Saturday. $35. Contact: Joan Covell, Med. Staff Sec., Daniel Freeman Memorial Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 672-0112, ext. 206.

December 6—**What Patients and Friends Ask About Asthma.** UCLA. Saturday.

December 6-11—**American Academy of Dermatology.** Hilton Hotel, San Francisco. Saturday-Thursday. Contact: Betty Suor, Exec. Dir., AAD, 1116 S. Fifth, Tacoma, Wa. 98405. (206) 572-4747.

December 7-9—**Advances in Heart Disease—1976.** American College of Cardiology at Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 10—**Colloquia in Cardiology—No. 8: Stress and the Heart—The Influence and Management of Stress in Heart Disease.** American College of Cardiology at Ambassador Hotel, Los Angeles. Wednesday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 10-12—**Respiratory Failure.** USC. Wednesday-Friday.

January 16—**Current Concepts in Management of Thyroid Disorders.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Friday. Contact: Linda Alperstein, Coord., CME, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

February 5-6—**Contact Dermatitis.** STAN. Thursday-Friday.

February 14—**Annual Cardiology Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

February 16-21—**Topics in Internal Medicine.** UCSD at Town and Country Hotel, San Diego. Monday-Saturday.

February 26-27—**Dermatology for Internists and General Practitioners.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

February 26-28—**Pediatric Hematology.** See Pediatrics, February 26-28.

February 27-28—**Pulmonary Artery Catheterization.** PMC. Fri.-Sat.

OBSTETRICS AND GYNECOLOGY

December 13-14—**Birth and Rebirth.** UC Extension, Santa Cruz. Saturday-Sunday. 15 hrs. $40. Contact: Darla Chadima, Cont. Ed. Specialist, UC Extension, Santa Cruz 95064. (408) 429-2971.

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

January 16-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD at Sea Lodge, La Jolla. Friday-Monday.

January 17-24—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical & Gynecological Society at Beverly Hilton Hotel, Los Angeles. Saturday-Sunday. 14 hrs. $45. Contact: Miss Dee Davis, Exec. Sec., L.A. Ob & Gyn Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 18-20—**Neonatal Medicine.** USC. Wednesday-Friday.

February 24-26—**Ob Infectious Diseases.** USC. Tuesday-Thursday.

PEDIATRICS

November 15—**Pediatric Dermatology.** See Medicine, November 15.

November 22—**Management of Respiratory Failure in Infants.** Harbor General Hospital, Torrance. Saturday. 6 hrs. $45. Contact: Ellen Woolfson, Cont. Ed. Coordinator, Torrance General Hospital, 1124 W. Carson A-19, Torrance 90502. (213) 775-7711, ext. 1373.

December 6—**American Academy of Pediatrics, California Chapter 1, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

January 8-11—**Winter Ski and Study Symposium—First Annual.** American Academy of Pediatrics, Calif. Chapter 2, at Mammoth Mountain. Thursday-Sunday. 14½ hrs. $125. Contact: AAP, Calif. Chapter 2, P.O. Box 2134, Inglewood 90305.

January 23-25—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 23-25.

February 18—**The Pediatrician's Obligation in the Atherosclerosis Epidemic.** American Heart Assn., Greater L.A. Affiliate, and L.A. Pediatric Society at Hyatt Regency Hotel, Los Angeles. Wednesday. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 26-28—**Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty Calori, CHMC, 51st & Grove Sts., Oakland 94609.

PSYCHIATRY

December 10-13—**Development of Techniques for Family Counseling.** See Of Interest To All, December 10-13.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** USC. Wednesdays, 10:00 a.m.-12:00 noon.

February 1-6—**Psychiatry Update: 2nd Annual Mid-Winter Program for Psychiatrists.** UCD at Bear Valley. Sunday-Friday.

RADIOLOGY AND PATHOLOGY

December 3-7—**California Society of Pathologists—Annual Meeting.** Hyatt Regency, San Francisco. Wednesday-Sunday. Contact: Mr. Richard E. Hall, CSP, 1225 8th St., Suite 590, Sacramento 95814. (916) 446-6001.

December 11-14—**Fluid and Electrolytes.** USC at Tennis Club, Palm Springs. Thursday-Sunday.

December 13—**Principles and Procedures of Blood Gases.** PMC. Saturday. $65.

January-May—**Ultrasound — Comprehensive Lecture Series.** USC. Weekly, 7:00-9:00 p.m., 20 consecutive weeks. Contact: Robert L. Wilson, MD, P.O. Box 1961, 1200 N. State St., Los Angeles 90033.

January 30-February 1—**Midwinter Radiological Conference—28th Annual.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Los Angeles Radiological Society, 15107 Vanowen St., Van Nuys 91405.

SURGERY AND ANESTHESIOLOGY

November 15—**Current Concepts in Ophthalmic Plastic Surgery: The Eye Lid.** UCLA. Saturday.

November 15—**Anesthesia and the Blood.** UCD at Woodlake Inn, Sacramento. Saturday.

November 21-23—**Common Problems—Acute Hand Injuries.** UCLA. Friday-Sunday.

November 22—**Flexible Bronchofibroscopy.** PMC. Friday. 6 hrs. $300.

December 3-5—**Hereditary Disorders of the Eye—Annual Ophthalmology Course.** UCSF. Wednesday-Friday.

December 5—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. $150. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** See Of Interest To All, December 5-6.

December 5-7—**Electronystagmography.** PMC at Regency Hyatt, San Francisco. Friday-Saturday.

December 5-9—**International College of Surgeons, U.S. Section—Annual Meeting.** Sheraton Waikiki, Honolulu. Friday-Tuesday. Contact: Mr. William A. Houser, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago. Ill. 60610. (312) 642-3555.

December 8-12—**Postgraduate Institute for Emergency Physicians.** See Of Interest To All, December 8-12.

December 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** See Psychiatry, January 7-March 17.

January 8-9—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 9—**Vitreal and Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

January 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

January 11-17—**Otologic Surgery Course.** Ear Research Institute, Los Angeles. One week. 48 hours. $550; $350 for residents. Contact: F. H. Linthicum, Jr., MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 16-18—**Third Neonatal Respiratory Symposium.** California Society of Anesthesiologists at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

January 23-25—**Pediatric Anesthesiology—14th Clinical Conference.** Childrens Hospital of L.A. at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, CHLA, P.O. Box 54700, Los Angeles 90054. (213) 663-3341, ext. 2262.

January 25-30—**Postgraduate Institute on Emergency Medicine.** See Of Interest To All, January 25-30.

January 26-30—**Topics in Emergency Medicine.** See Of Interest To All, January 26-30.

January 28-30—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 1-4—**Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday.

February 5-6—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 6—**Photocoagulation Therapy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

February 11-13—**Clinical Applications of Vitreous Surgery.** USC. Wednesday-Friday.

February 12-15—**Symposium on Controversial Areas in Surgery of the Head and Neck—5th Annual.** UCSD. Thursday-Sunday. Contact: UCSD or Alan M. Nahum, MD, University Hospital, 225 W. Dickinson, San Diego 92103.

February 13-14—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

(Continued on Page 40)

DARVOCET-N® 100

propoxyphene napsylate with acetaminophen

Indication: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

DARVON® COMPOUND-65

propoxyphene hydrochloride, aspirin, phenacetin, and caffeine

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Salicylates may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375]

500389

Additional information available to the profession on request.

Eli Lilly and Company, Inc.
Indianapolis, Indiana 46206

Relief from her arthritic pain

Darvocet-N® 100

100 mg. propoxyphene napsylate and 650 mg. acetaminophen

contains no aspirin

Darvon® Compound-65

65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine

contains aspirin

for mild to moderate pain

See summary of prescribing information on adjoining page.

(Continued from Page 38)

OF INTEREST TO ALL PHYSICIANS

November 15-16—**Crises Intervention—Part I.** UCLA. Saturday-Sunday.

November 20-22—**American Association for Automotive Medicine.** Sheraton Harbor Island, San Diego. Wednesday-Saturday. Contact: Albert Carriere, 801 Green Bay Rd., Lake Bluff, Ill. 60044.

November 30-December 4—**American Medical Association—29th Clinical Convention.** Sheraton Waikiki, Honolulu. Sunday-Thursday. Contact: AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

December 4-6—**Rheumatic Diseases—4th Annual Western Regional Conference.** UCSF at Claremont Hotel, Oakland. Thursday-Saturday.

December 5-6—**Invitational Seminar: Clinical Aspects of Common Infectious Disease.** Eisenhower Medical Center, Palm Desert. Friday-Saturday. 8 hrs. $50. Contact: Office of Medical Education, Eisenhower Medical Center, Palm Desert 92260. (714) 346-3911.

December 8-12—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD. Monday-Friday.

December 10-13—**Development of Techniques for Family Counseling.** UCLA at Marina City Club, Marina Del Rey. Wednesday-Saturday.

December 13-14—**Crises Intervention—Part II.** UCLA. Saturday-Sunday.

January 8-9—**New and Old Antibiotics.** USC. Thursday-Friday.

January 21-24—**The Physician and the Hospital.** USC at Canyon Hotel, Palm Springs. Wednesday-Saturday.

January 23-24—**Management of Stress in the Middle Years.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123.

January 25-30—**Postgraduate Institute on Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sunday-Friday.

January 26-30—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 6-11—**California Medical Association—105th Annual Session.** Hyatt Regency Hotel, San Francisco. Friday-Wednesday.

February 10-14—**Autogenics Training Techniques Workshop.** UCLA at Lake Arrowhead. Tuesday-Saturday.

February 13-14—**Diving Medicine for Practicing Physicians.** UCSF at Holiday Inn-Union Square, San Francisco. Friday-Saturday.

February 15-19—**Sports Medicine for Primary Physicians.** Hawaii Medical Association at Lihue, Kauai, Hawaii. Monday-Thursday. Contact: HMA Emergency Medical Service Program, 1301 Punchbowl St., Honolulu 96813.

February 28-29—**Infectious Disease and Pulmonary Disease for Family Practitioners.** UCLA. Saturday-Sunday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal displays, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, Auditorium, Providence Hall, 700 N.E. 47th Avenue, Portland, 97213

November 19—**Constipation and Laxative Abuse.**

November 26—**The Difficult Patient.**

December 10—**Grans vs. Scans in Diagnosis of Pulmonary Thromboembolic Disease.**

December 17—**Hepatitis A, Hepatitis B, and Thee.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

(Continued from Page 34)

SITUATIONS WANTED

UROLOGIST, 29, completing top university residency July, 1976, seeks solo, group, or partnership. All situations considered. Box 9449, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST WITH PULMONARY SUBSPECIALTY. Extensive training in fiberoptic bronchoscopy and setting up and operating P.F.T. lab, respiratory therapy unit. Board/eligible. Flexible. California licensed. Seeks hospital based clinic appointment preferably with academically stimulating group on coastal California. Write Box No. 9453, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRIC LOCUM TENENS WORK WANTED. 36-year-old board certified pediatrician licensed California, Alaska. Available March 1976. T. McCabe, MD, 530 Webster St., Palo Alto, CA 94301.

PRACTICES FOR SALE

EENT practice established 54 years ago, for sale in Vallejo, California, 1727 Sonoma Blvd., 94590. Telephone (707) 643-4415, John W. Green, MD.

600 ACRE RANCH IN SECLUDED VALLEY

In the hills just 7 miles west—the cooler side—of Healdsburg in picturesque Sonoma County. Convenient 75 miles north of San Francisco over scenic Redwood Highway 101 Freeway. Nearby shopping Healdsburg and Santa Rosa, yet secure and out of the way. Scattered meadows, oaks, redwoods and firs. Superb views. Wallace Creek flows through. Several springs, fine underground water. Fenced and cross fenced. Main ranch house 6 rooms, barn, corrals, manager's cottage, and lake. Deer, wild pig and other game. Perfect hide-a-way for troubled times ahead. Only $600 per acre—compare with Sierra and desert property values. Contact owner (415) 453-3805, or your broker.

OFFICES FOR LEASE OR RENT

MEDICAL SUITE FOR GROUP PRACTICE—Up to 4,000 sq. feet to be available in January, 1976. Located in South San Francisco. Reply Box No. 9431, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

MEDICAL SUITE AVAILABLE, NOVEMBER 1, 1975, in the Foothill Medical Building, 21297 Foothill Blvd., Hayward, CA 94541. It consists of 850 sq. ft., 3 treatment rooms, waiting room, nurses station and private doctor's office. The building has an x-ray and medical laboratory, and a pharmacy. It is currently occupied by Family Practice Physicians predominantly. For information call (415) 582-6942.

CALIFORNIA—SAN FRANCISCO—Unique, new professional building in central, beautiful, growing suburb of Bay Area. Custom design your own suite in modern facility with 15 general practitioners and specialists. Space available immediately. Contact Westborough Professional Center, Suite 204, 2400 Westborough Boulevard, South San Francisco, CA 94080; (415) 873-8286.

OF INTEREST TO ALL PHYSICIANS

November 12—**Geriatric Psychiatry.** University of Oregon Health Sciences Center, School of Medicine Hospital, Lecture Room 8B60. Contact: Judith A. Scholz, Health Center for the Elderly, 1710 N.E. 42nd Avenue, Portland, 97213.

November 19—**A Transactional View of the Aging Process.** University of Oregon Health Sciences Center, School of Medicine Hospital, Lecture Room 8B60. Contact: Judith A. Scholz, Health Center for the Elderly, 1710 N.E. 42nd Avenue, Portland, 97213.

November 26—**Clinical Geriatrics.** University of Oregon Health Sciences Center, School of Medicine Hospital, Lecture Room 8B60. Contact: Judith A. Scholz, Health Center for the Elderly, 1710 N.E. 42nd Avenue, Portland, 97213.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

November 13-14—**Current Concepts in Drug Therapy.** Thursday-Friday. Univ. of Wash. Health Sciences Center, Seattle. 12 hrs. $50. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch of Med., Seattle 98195. (206) 543-1050.

November 14-15—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 4-5—**Life Saving Measures for the Critically Injured. (A.C.S.)** Thursday-Friday. Washington Plaza Hotel, Seattle. Limited to 200. 15 hrs. Practitioners, $150; interns, residents, $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

December 4-5—**Pacific Northwest Chapter, American College of Chest Physicians: Scientific Program.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 12-13—**Clinical Problems in Endocrinology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 9-10—**Laboratory Investigations in Gastrointestinal Disease.** Friday-Saturday. Virginia Mason Medical Center Auditorium. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 22-23—**Pediatric Allergy and Immunology.** Thursday-Friday. Univ. of Wash., Child Development and Mental Retardation Center, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 30-31—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Olympic Hotel, Seattle. Limited to 50 physicians and spouses. 12 hrs. $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. School of Med., Seattle 98195. (206) 543-1050.

February 5-7—**Stroke Symposium.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 12 hrs. Physicians, $40; others, $25. Contact: Northwest Hospital, 1551 North 120th, Seattle 98133. (206) EM 4-0500.

February 6-12—**Critical Care: Maternal and Perinatal.** Friday-Thursday. Sun Valley, Idaho. 21 hrs. MDs, PhDs, $100; others, $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 12-13—**14th Annual Symposium on Respiratory Disease.** Friday-Saturday. Olympic Hotel, Seattle. 14 hrs. $15. Contact: Ms. Jo Senters, Washington Lung Association, 216 Broadway East, Seattle 98102. (206) 322-7110.

February 18-19—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Longview, 18; Olympia, 19. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050.

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contains natural estrogens exclusively and also meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

BRAND OF CONJUGATED ESTROGENS TABLETS, U.S.P.

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

INFECTIOUS DISEASES: Epidemiology and Clinical Practice—Second Edition—A. B. Christie, MD, FRCP, FFCM, DPH, DCH, Senior Consultant Physician in Infectious Diseases, Fazakerley Hospital, Liverpool, Consultant in Smallpox, Department of Health and Social Security, President, Association for the Study of Infectious Disease. Churchill Livingstone, Edinburgh, London and New York, 1974. Distributed in the USA by Longman Inc., 72 Fifth Avenue, New York City (10011). 1,095 pages, $42.00.

IS IT WELL WITH THE CHILD?—A Parent's Guide to Raising a Mentally Handicapped Child—Susan Strauss. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1975. 152 pages, $7.95.

MEDICAL EXAMINATION REVIEW BOOK—Volume 7A—Textbook Study Guide of Psychiatry—James R. Allen, MD, Associate Professor of Psychiatry and Behavior Science, Associate Professor of Human Ecology; and Barbara Ann Allen, MSW, PhD, Formerly, Instructor in Psychiatry, University of Oklahoma, Health Sciences Center, Oaklahoma City. Medical Examination Publishing Company, Inc., 65-36 Fresh Meadow Lane, Flushing, NY (11365), 1975. 144 pages, $7.50.

NON-INVASIVE METHODS IN CARDIOLOGY—Edited by Samuel Zoneraich, MD, Associate Professor of Medicine, State University of New York at Stony Brook Health Sciences Center, School of Medicine; Head, Division of Cardiology, Queens Hospital Center, The Long Island Jewish-Hillsdale Medical Center. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62703), 1975. 583 pages, $35.50.

NUCLEAR MEDICINE IN CLINICAL PEDIATRICS—Edited by Hirsch Handmaker, MD, Director, Nuclear Medicine, Children's Hospital of San Francisco; and Jerold M. Lowenstein, MD, Chairman, Department of Nuclear Medicine, Pacific Medical Center, San Francisco. Publishing Sciences Group, Inc., 411 Massachusetts Avenue, Acton, MA (01720), 1975. 296 pages, $22.50.

PHYSICAL EXAMINATION OF THE SURGICAL PATIENT—An Introduction to Clinical Surgery—Fourth Edition—J. Engelbert Dunphy, MD, Professor of Surgery, University of California, San Francisco; and Thomas W. Botsford, MD, Associate Professor of Surgery, Harvard Medical School, Surgeon, Peter Bent Brigham Hospital, Boston. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 414 pages, $16.00.

PRACTICAL MANUAL OF PEDIATRICS—William W. Waring, MD, Professor of Pediatrics and Chief of Section of Pulmonary Diseases, Department of Pediatrics, Tulane University School of Medicine, New Orleans; Louis O. Jeansonne III, MS, MD, Instructor, Department of Pediatrics, Tulane University School of Medicine, Chief Resident, Department of Pediatrics, Charity Hospital of Louisiana, New Orleans. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1975. 343 pages, $5.95.

PRACTICE OF SURGERY—Current Review—Volume II—Walter F. Ballinger, MD, Bixby Professor of Surgery and Head of the Department, Washington University School of Medicine, St. Louis; and Theodore Drapanas, MD, Henderson Professor and Chairman of the Department of Surgery, Tulane University School of Medicine, New Orleans. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis (63103), 1975. 500 pages, $29.50.

THE RIGHTS OF HOSPITAL PATIENTS—The Basic ACLU Guide to a Hospital Patient's Rights—George J. Annas, Director of the Center for Law and Health Sciences, Boston University School of Law. Avon Books, 959 Eighth Avenue, New York City (10019), 1975. 246 pages, $1.50 (Paperback).

Index to The Western Journal of Medicine Advertising

Audio-Digest Foundation 21

Ayerst Laboratories
Premarin 42, 43

Books Received 44

Burroughs Wellcome Co.
Empirin Compound with Codeine 13
Neosporin Topical 29

Classified 32, 34, 41

CMA-105th Annual Session and Western Scientific Assembly
Hotel Accommodations 33

Dairy Council of California 35

Geigy Pharmaceuticals
Butazolidin 17, 18

Eli Lilly & Company
Nebcin 14, 15, 16
Keflex 28
Darvon-N 100 and Darvon Compound-65 .... 38, 39

Medical Ancillary Services Inc. 19

Merck Sharp & Dohme
Aldomet 4, 5, 6
Triavil 22, 23, 24

Obetrol Pharmaceuticals
Obetrol 25

Pharmaceutical Manufacturers Association 10, 11

Presto Food Products Inc.
Mocha Mix 3

PVO International
Saffola 7

Roche Laboratories
Gantanol 8, 9
Valium ..... 2nd Cover and Page 1

William H. Rorer, Inc.
Maalox ..... 4th Cover

G. D. Searle & Co.
Lomotil 12, 13

Smith Kline & French
Dyazide ..... 3rd Cover

Wyeth Laboratories
Bicillin/Wycillin 26, 27
Ovral 31

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970: Section 3685, Title 39, United States Code for THE WESTERN JOURNAL OF MEDICINE, published monthly at San Francisco, California, for September, 1975.

1. Location of known office of publication: 731 Market Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 731 Market Street, San Francisco, California, 94103.

3. Publisher: California Medical Association, 731 Market Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 731 Market Street, San Francisco; Managing Editor, David Greer, 731 Market Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 731 Market Street, San Francisco, California 94103 (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities. There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total, 31,470: paid circulation by mail subscription, 29,783; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 1,296; total distribution, 31,079; office use, leftover, unaccounted, spoiled after printing, 391; total net press run, 31,470. Single issue nearest to filing date, September, 1975; Total, 30,137; paid circulation by mail subscriptions, 29,323; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 517; total distribution, 29,840; office use, leftover, unaccounted, spoiled after printing, 297; total net press run, 30,137. David Greer, Managing Editor.

Refer to: Levin PM, Shore EH, Treiman RL, et al: Ruptured abdominal aortic aneurysms—Surgical treatment. West J Med 123:431-435, Dec 1975

THE WESTERN
Journal of Medicine

Ruptured Abdominal Aortic Aneurysms

Surgical Treatment

PHILLIP M. LEVIN, MD; ERNEST H. SHORE, MD;
RICHARD L. TREIMAN, MD, *and* ROBERT F. FORAN, MD, *Los Angeles*

The records of 62 consecutive patients with ruptured abdominal aortic aneurysms were analyzed to determine what factors contribute to lower mortality. Survival was directly related to the immediate preoperative hemodynamic status of the patients. In 18 cases in which operation was carried out with patients stable, 83 percent of the patients survived. Even if shock was present by the time of operation (37 cases), a 68 percent survival rate was achieved. Cardiac arrest occurred before obtaining aortic control in seven patients and one survived.

Survival rates were increased if certain preoperative, operative and postoperative guidelines were followed. Since the combined operative mortality and late graft failure rate in 125 elective aneurysmectomies done during the same decade was under 5 percent, all abdominal aortic aneurysms with few exceptions should be surgically treated before rupture occurs.

RUPTURED ABDOMINAL AORTIC ANEURYSMS are associated with high mortality rates. Despite modern surgical techniques, the operative mortality reported for patients undergoing repair of this condition during the last decade has ranged from 40 to 80 percent.[1-13] The experience of DeBakey,[14] Mannick[15] and more recently Chiariello[16] indicates that a higher rate of survival can be obtained. We have reviewed our experience with ruptured abdominal aortic aneurysms to determine what clinical and technical factors contribute to lower mortality and what areas of management require further improvement.

From Cedars-Sinai Medical Center, Los Angeles.
Submitted July 14, 1975.
Reprint requests to: Phillip M. Levin, MD, Vascular Surgery Associates Medical Group, 435 North Bedford Drive, Beverly Hills, CA 90210.

Clinical Data

From October 1964 to October 1974 the authors operated upon 62 patients with ruptured abdominal aortic aneurysms. During the same period 125 elective aneurysmectomies were done.

All ruptured aneurysms were infrarenal in location with extravasation of blood into the retroperitoneal tissues or into the free peritoneal cavity. There were no ruptures into either the inferior vena cava or lumen of the bowel. Patients with acutely expanding aneurysms or with dissecting aneurysms involving the abdominal aorta were not included. There was one patient with a false aneurysm of a previously placed aortic homograft.

The series included 52 men and 10 women. The average age at time of rupture was 70 years, with

the oldest patient being 85 and the youngest 58. Age distribution by decade is shown in Table 1.

Initial symptoms of rupture customarily included sudden severe back pain or abdominal pain, often accompanied by nausea and vomiting. When pain radiated to the flank, groin or scrotum, confusion as to the correct diagnosis frequently resulted. The correct diagnosis was promptly established when a combination of back or abdominal pain (or both), mild or severe shock, and a pulsatile abdominal mass was recognized.

The duration of symptoms before admission to hospital is indicated in Table 2. In several cases the diagnosis was obscure because the patients had a history of several days to weeks of back or abdominal pain without evidence of shock or of a pulsatile mass. In many patients the initial period of weakness and shock was followed by a variable period (several hours to several weeks) of recovery of cardiovascular stability before final exsanguinating-type hemorrhage occurred. In others, with massive extravasation of blood, shock was profound from the onset of symptoms and never spontaneously regressed.

The sequence of retroperitoneal hemorrhage, tamponade and rebleeding determines the immediate preoperative hemodynamic status of the patients with ruptured abdominal aortic aneurysms (Table 3). Eighteen patients were considered stable at the time of operation, while 37 patients were in shock, and 7 patients sustained a cardiac arrest before obtaining aortic control.

Thirteen patients in the series had a known diagnosis of abdominal aortic aneurysm before admission to hospital. The distinct borders that one may palpate in intact aneurysms are often obliterated after rupture. The resulting diffuse and vague outline of the pulsatile mass makes diagnosis more difficult especially in obese patients, where diffuse tenderness may be the principal abdominal finding.

Results

The effect of the patient's immediate preoperative hemodynamic status upon survival is shown in Table 3. In 18 cases in which operation was carried out with patients stable, 83 percent of the patients survived. If shock was present by the time of operation (37 cases), a 68 percent survival rate was achieved. Cardiac arrest occurred before obtaining aortic control in seven patients; there was one survivor. During the same decade

TABLE 1.—*Age Distribution*

Age	*Patients*	*Died*	*Percent Survival*
80 and above	7	2	71
70-79	29	11	62
60-69	23	6	74
50-59	3	1	67

TABLE 2.—*Duration of Symptoms Before Admission to Hospital*

Time	*Patients*
Weeks	5
1-6 days	16
More than 12 hours	9
Less than 12 hours	17

TABLE 3.—*Relationship of Preoperative Hemodynamic Status to Survival*

Preoperative Hemodynamic Status	*Patients*	*Died*	*Percent Survival*
Ruptured	62	21	66
Cardiac arrest	7	6	14
Shock	37	12	68
Stable	18	3	83
Elective	125	5	96

TABLE 4.—*Mode of Management*

	Patients	*Survived*	*Died*	*Percent Survival*
Immediate operation	36	29	7	81
Delay for diagnostic studies or medical treatment or both	26	14	12	54

96 percent of 125 patients having elective aneurysmectomies survived.

The survival of patients with ruptured abdominal aortic aneurysms as related to their ages at the time of rupture is shown in Table 1. Seventy-one percent of the seven patients aged 80 and above survived surgical operation, while 62 percent of those patients in their 70's were able to leave the hospital. Seventy-four percent of patients in their 60's survived, and two of the three patients in their 50's had a successful outcome.

The general mode of management in this series of patients is shown in Table 4. When the diagnosis of a ruptured abdominal aortic aneurysm was made without delay, the patient was immediately taken to the operating room. All preoperative preparations were carried out in the operating suite before the induction of anesthesia. Of the 36 patients who received immediate operative treatment 81 percent survived. When diagnosis remained obscure (26 patients), various diagnostic tests or prolonged attempts to improve hemodynamic status were carried out before

recognition of the ruptured abdominal aortic aneurysm. Under these circumstances, there were 14 survivors (54 percent).

The postoperative complications encountered are listed in Table 5. Respiratory insufficiency and renal failure were the most common complications and frequently resulted in postoperative mortality. All patients with renal failure underwent acute hemodialysis and there were 11 tracheotomies done on patients with either pneumonitis or acute respiratory insufficiency. In four patients, jaundice developed in the early postoperative period but this complication never proved fatal. The incidence of myocardial infarction, cerebral-vascular accident and congestive heart failure was quite low. One patient had to be returned to the operating room because of postoperative bleeding. Pancreatic injury, ureteral injury, postoperative small bowel obstruction and perforated duodenal ulcer were infrequent isolated complications encountered in this series.

TABLE 5.—*Complications*

Type	*Number Patients*	*Associated with Postoperative Mortality*
Pneumonitis respiratory insufficiency	11	5
Renal failure	7	4
Jaundice	4	0
Myocardial infarction	1	1
Cerebral-vascular accident	2	1
Congestive heart failure	1	0
Pancreatic injury	1	0
Ureteral injury	1	0
Postoperative hemorrhage	1	1
Small bowel obstruction	1	0
Perforated duodenal ulcer	1	0

Discussion

The survival rate of 66 percent in a series of 62 patients with ruptured abdominal aortic aneurysms over the past decade is better than that found in many previous reports.[1-13] If those patients are excluded who had sustained a cardiac arrest before aortic control, the survival rate improves to 73 percent. Spontaneous tamponade of retroperitoneal hemorrhage results in a stable preoperative hemodynamic status. Under these circumstances survival (83 percent) approaches that of elective aneurysmectomy. These figures indicate that a more optimistic prognosis is possible for patients with ruptured abdominal aortic aneurysm if certain guidelines of preoperative, operative and postoperative management are followed.

Preoperative

This series clearly shows that early diagnosis followed by immediate operation is the essential factor if improved survival rates are to be obtained. This requires a high index of suspicion on the part of internists and general practitioners, as well as surgeons, when an elderly patient presents with a history of acute back or abdominal pain and signs of circulatory instability. Unnecessary and potentially harmful diagnostic studies must be avoided. When immediate operation was undertaken in 36 patients, 29 (81 percent) survived. This contrasts with 26 other patients in whom surgical operation was delayed, resulting in a decreased survival rate of only 54 percent. It is noteworthy that 13 patients in this series had a known prior history of an abdominal aortic aneurysm before they presented with rupture. In eight of these patients an early diagnosis was made and operation was undertaken immediately—with seven survivors. However, among the five other patients the correct diagnosis was not established despite the knowledge of an aneurysm being present. Various diagnostic tests were undertaken before the patient reached the operating room and four of these patients died.

As soon as the diagnosis is established the patient should be taken to the operating room and all further preparations made there. Restoration of normovolemia by rapid infusion of blood or colloid frequently results in renewed hemorrhage. Therefore, except for patients in danger of cardiac arrest from exsanguination, massive fluid administration should be withheld until infrarenal aortic control has been obtained. Anesthesia should not be induced until the surgeons are in total readiness, for general anesthesia will frequently deepen shock or precipitate acute collapse in a seemingly compensated patient. The insertion of bladder catheters, central venous pressure monitoring lines and venous cutdowns, and the obtaining of blood for typing and cross-matching must not delay operation but should be carried out concurrently, as rapid control of the aorta followed by restoration of circulatory volume are the immediate requirements for a successful outcome.

When an operating room is not immediately available, a circumferential G-suit may temporarily control intraabdominal bleeding.[17] In addi-

tion, the external counterpressure provided by a G-suit may increase arterial pressure from nondiscernible to low-normal levels, allowing more time for preparation of the operating room.

Operative Management

The technique of resection of a ruptured abdominal aortic aneurysm has not changed in the past decade. Immediate control of the infrarenal aorta, limited anterior resection of the aneurysm and wrapping the aneurysm wall over the prosthetic graft as a protective cover was practiced in all of these cases. Deliberate left thoracotomy or suprarenal occlusion for aortic control has not been necessary. These methods are frequently ineffective and have been associated with unnecessary complications. Rapid but careful finger dissection in the retroperitoneal hematoma with visual identification of the infrarenal aorta is the best method for obtaining aortic control. Insertion of balloon catheters into the proximal aorta has not been necessary and may cause renal complications by forcing atheromatous material or clot into the renal arteries.

Immediately before achieving aortic control the patient is heparinized and blood replacement is started along with the infusion of mannitol. Although controversy still exists regarding the efficacy of mannitol in preventing renal shutdown after aortic operation, there is considerable experimental evidence that mannitol does increase renal perfusion during hypotension.[18-20] If restoration of normovolemia and infusion of mannitol do not achieve diuresis during the operation, furosemide (Lasix®) is also administered.

During the operative procedure, several factors tend to produce hypothermia. Profound hypothermia can be avoided by placing a large heating blanket beneath the patient before operation and by running all intravenous fluids through heating units. In addition, heat loss from the peritoneal cavity can be diminished by irrigating the abdomen with warm solutions.

Two technical points that deserve emphasis are the secure control of retroperitoneal bleeding and bypass of associated iliac occlusive disease when encountered. Only one patient in this series had to be returned to the operating room for postoperative hemorrhage and this complication was contributory to the patient's death. If massive transfusion has been necessary, the use of protamine sulfate alone may not be sufficient to establish normal coagulation. Fresh whole blood, fresh frozen plasma and platelet packs should be appropriately administered if a coagulopathy has developed. However, careful exploration and the secure control of all bleeding points must be accomplished before continued oozing is attributed to a coagulation defect.

Survival is not influenced by the type of prosthetic graft employed. Woven dacron grafts are preferred over knitted dacron because of reduced bleeding through the interstices. There does not appear to be any difference in survival if either a tube or bifurcated graft is used. Of more importance is the decision to bypass significant iliac artery disease if it is present. Aortofemoral bypass should be done whenever necessary rather than attempting anastomosis of a graft limb to an unsuitable iliac artery. The additional operating time required is inconsequential compared to reoperation for an ischemic limb on a critically ill patient.

Postoperative Management

During the immediate postoperative period continuous assisted ventilation with a volume respirator is almost always necessary and has been extremely helpful in preventing early postoperative respiratory insufficiency. Assisted ventilation by either oral or nasotracheal tubes should be continued if the patient's arterial blood gas measurements reflect hypoventilation. If respiratory support is still necessary after two or three days, tracheostomy is indicated. Tracheostomy during the early postoperative period may ultimately improve chances of survival because it permits better tracheal toilet and avoidance of the depressive medications which are required to keep the patient on an endotracheal tube.

Almost all patients recovering from hypovolemic shock secondary to aneurysmal rupture have at least some mild degree of acute tubular necrosis. If the use of intravenous colloid and furosemide during the early postoperative phase does not result in an appropriate diuresis or if urinary function continues to decline, the patient should receive hemodialysis to avoid the generalized complications of uremia. The anticoagulation required for dialysis does not usually pose a bleeding problem in the patient three to four days following aortic surgery.

It is clear on the basis of this experience that early diagnosis and operation are the most important factors in increasing survival following rupture of an abdominal aortic aneurysm. Con-

trary to some reports, advanced age is not per se a deterrent to achieving survival in this group of patients.[21] Certain technical factors contribute to survival as described above. Early use of tracheostomy and hemodialysis can lead to improved survival if postoperative respiratory insufficiency or renal failure has developed.

The ratio of ruptured to unruptured abdominal aortic aneurysms is still too high in our experience and reflects a reluctance on the part of some physicians to recommend elective surgical operation for patients with an abdominal aortic aneurysm. Since the combined operative mortality and late graft failure rate with elective aneurysmectomy is under 5 percent, all abdominal aortic aneurysms with few exceptions should be surgically treated before rupture occurs.

REFERENCES

1. Hardin CA: Survival and complications after 121 surgically treated abdominal aneurysms. Surg Gyneco/Obstet 118:541-544, 1964

2. Sanger PW, Robicsek F, Taylor FT, et al: Ruptured aneurysm of the abdominal aorta. North Carolina Med J 25:501-506, 1964

3. Martin P: Ruptured abdominal aortic aneurysm. Proc Royal Coll Surg Eng 867-868, 1965

4. Tracy GD, Reeve TS: Mortality factors in aortic aneurysms. Aust New Zeal J Surg 35:85-93, 1965

5. Lawrence MS, Crosby VG, Ehrenhaft JL: Ruptured abdominal aortic aneurysm. Ann Thorac Surg 2:159-165, 1966

6. Szilagyi DE, Smith RF, DeRusso FJ, et al: Contributions of abdominal aortic aneurysmectomy to prolongation of life—Twelve-year review of 480 cases. Ann Surg 164:678-699, 1966

7. Kouchoukos NT, Levy JF, Butcher HR Jr: Mortality from ruptured abdominal aortic aneurysm. Am J Surg 113:232-235, 1967

8. Graham AL, Najafi H, Dye WS, et al: Ruptured aortic aneurysm. Arch Surg 97:1024-1031, 1968

9. Gwinn CB, Oury JH: A review of abdominal aneurysms at the Naval Hospital, San Diego, California. Am Surg 34:142-144, 1968

10. Berne TV, Wilkinson G: Ruptured abdominal aortic aneurysm. Am Surg 35:36-39, 1969

11. Van Heeckeren DW: Ruptured abdominal aortic aneurysm. Am J Surg 119:402-407, 1970

12. Darling RC: Ruptured arteriosclerotic abdominal aortic aneurysm. Am J Surg 119:397-401, 1970

13. Alpert J, Brief DK, Parsonnet V: Surgery for ruptured abdominal aortic aneurysm. JAMA 212:1355-1359, 1970

14. DeBakey ME, Crawford ES, Cooley DA, et al: Aneurysms of abdominal aorta—Analysis of graft replacement therapy 1-11 years after operation. Ann Surg 160:622-638, 1964

15. Mannick TA, Brooks JW, Bosher LH Jr, et al: Ruptured aneurysm of the abdominal aorta. N Engl J Med 271:915-920, 1964

16. Chiariello L, Reul GJ Jr, Wukasch DC, et al: Ruptured abdominal aortic aneurysm—Treatment and review of 87 patients. Am J Surg 128:735-738, 1974

17. Ludewig RM, Wangensteen SL: Aortic bleeding and the effect of external counterpressure. Surg Gyneco/Obstet 128:252-258, 1969

18. Beall AC Jr, Holman MR, Morris GC Jr, et al: Mannitol-induced osmotic diuresis during vascular surgery—Renal hemodynamic effects. Arch Surg 86:34-42, 1963

19. Peters G, Brunner H: Mannitol diuresis in hemorrhagic hypotension. Am J Physiol 204:553-562, 1963

20. Powers SR Jr, Boba A, Hostnik W, et al: Prevention of postoperative acute renal failure with mannitol in 100 cases. Surgery 55:15-22, 1964

21. Edmunds LH: Resection of abdominal aortic aneurysm in octogenarians. Ann Surg 165:453-456, 1967

Medical Treatment of Duodenal Ulcer

. . . By taking antacid one and three hours after a meal (if the patient will take the medicine), gastric acidity is maintained at low level for some three to four hours after a meal. I must emphasize, though, that while this is possible to do in a hospital, it is difficult with patients when they return home. Generally speaking, patients do not take antacids when they are prescribed to them over long periods. Some data: Roth and Burger in 1960 studied patients in hospital who had antacids prescribed for them (generally the amount of antacid ordered was eight ounces per day); when they analyzed how much was taken by the patient, it was only about 3½ ounces per day, or about 42 percent of that which was prescribed. This was in a hospital and if that happens in a hospital, I am sure it is much worse at home. I want to emphasize, however, that I think with the proper kind of doctor-patient relationship and with proper instruction and emphasis to the patient, we can do much better than that, but this remains to be proved.

—JOHN S. FORDTRAN, MD, *Dallas*

Extracted from *Audio-Digest Internal Medicine,* Vol. 22, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Meares EM Jr: Infectious urethritis in men and women —Diagnosis and treatment. West J Med 123:436-440, Dec 1975

Infectious Urethritis in Men and Women

Diagnosis and Treatment

EDWIN M. MEARES, JR., MD, *Boston*

Acute and recurrent infectious urethritis in men and women is commonly seen by physicians. Since specific therapy varies widely with the type of urethritis present, the proper diagnosis must be clearly established if curative drug therapy is to be selected. It is valuable, therefore, to review the diagnosis and therapy of the various forms of infectious urethritis that are recognized today in both men and women.

VARIOUS TYPES of acute and recurrent urethritis in men and women are frequently seen by practicing physicians. Urethritis is probably most commonly treated, at least initially, by a general practitioner or family physician. The success or failure of cure depends upon the proper recognition of the type of urethritis present and the selection by the physician of the proper course of therapy. Because of the frequent occurrence of urethritis in patients and because we frequently see patients in consultation who have not been cured by the physician first seen, it seems timely to review the types of infectious urethritis that are recognized today and to suggest specific therapy according to the specific type of disease that is diagnosed.

Uncomplicated Gonorrhea

During the past 20 years in the United States, the incidence of acute cases of gonorrhea has shown a pronounced increase. The disease is vastly underreported and it has been estimated that in the United States one new infection with Neisseria gonorrhoeae occurs approximately every two minutes.[1] Man is the only known host for N. gonorrhoeae and transmission is virtually exclusively through sexual means, the exceptions being gonococcal ophthalmia of the newborn and gonococcal vulvovaginitis of prepubertal girls, which is considered to be a fomite-spread infection.

In men the anterior urethra and periurethral glands are the sites of primary involvement. An acute, purulent exudate occurs (urethral discharge), which consists of polymorphonuclear leukocytes, many bearing engulfed gonococcal organisms. Without therapy, the posterior urethra and eventually the prostatic ducts may become involved. Inadequately treated gonococcal urethritis may result in periurethral abscess formation and eventually urethral stricture. Late complications include bacteremia, acute epididymitis, septic arthritis, skin lesions, endocarditis and tenosynovitis.

In women the sites most commonly involved initially are the urethra and cervix. Early in acute cases a purulent vaginal discharge occurs. Early involvement of the periurethral glands, the Skene and Bartholin glands, and the labia may be seen. Without early treatment the inflammatory reaction can spread to the endometrium, the fallopian tubes and the ovaries in a fulminating pelvic in-

From the Division of Urology, Department of Surgery, Stanford University School of Medicine, Stanford, California.

Dr. Meares, formerly of Stanford, is now Professor of Surgery and Chairman, Department of Urology, Tufts University School of Medicine, New England Medical Center Hospital, Boston.

Submitted July 7, 1975.

Reprint requests to: Department of Urology, Tufts University School of Medicine, New England Medical Center Hospital, 171 Harrison Avenue, Boston, MA 02111.

flammatory disease. Late complications include those stated for men, in addition to sterility, ectopic pregnancy and hydropyosalpinx.

Gonorrhea of the rectum can occur in either sex and pharyngeal gonorrhea is being seen with increasing frequency today in both homosexuals and in heterosexuals who engage in oral sex.

Diagnosis

The diagnosis of gonorrhea is made by the demonstration of N. gonorrhoeae in Gram stain smears and its isolation in suitable culture media. Specimens of discharge should be subjected to a Gram stain: the presence of Gram-negative diplococci that are intracellular is diagnostic and is about 99 percent reliable in cases of acute urethritis. Specimens of the discharge should also be streaked onto chocolate agar, or preferably onto Thayer-Martin vancomycin-colistin-nystatin (VCN) medium and incubated for at least 48 hours in a candle jar or in a CO_2 incubator. Confirmation of the diagnosis in women by laboratory means is more difficult than in men. Early in the course of the disease, in the presence of a purulent discharge, a Gram stain of the exudate may be diagnostic; however, if a subacute or chronic infection is present with no signs or symptoms of disease, the smear is unreliable and culture methods are essential. Duplicate swabs (one for smear and one for culture) should be obtained from the vagina, urethra, cervix and rectum in women.

In cases where the diagnosis may be difficult or inconclusive by smear and culture techniques, a fluorescent antibody procedure, which was developed by Peacock and associates[2] may be helpful.

Treatment

The following forms of treatment for uncomplicated gonorrhea, whether it be urethral, cervical, pharyngeal or rectal, have been recommended by the Venereal Diseases Branch of the Center For Disease Control, Atlanta, Georgia.[3]

Parenteral. In both men and women, aqueous procaine penicillin G, 4.8 million units, should be given intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of probenicid given orally, preferably at least 30 minutes before the penicillin injection.

Oral. In both men and women, ampicillin, 3.5 grams, with probenecid, 1 gram, should be administered simultaneously.

When Penicillin and Ampicillin Are Contraindicated or Are Ineffective

Parenteral. In men, spectinomycin (Trobicin®), 2 grams in one intramuscular injection should be given. In women, spectinomycin, 4 grams, should be given in one intramuscular injection.

Oral. In both men and women, 1.5 grams of tetracycline hydrochloride should be given initially, followed by 0.5 gram every six hours for four days—for a total dosage of 9 grams. Other tetracyclines may be used, but have not to date been found to be more effective. As an alternate treatment in men,[4] trimethoprim-sulfamethoxazole (Septra®, Bactrim™), six tablets once daily for three days, may be given.

Follow-up. In men, urethral cultures should be done seven days after therapy has been completed. In women, cervical and rectal cultures should be done 7 to 14 days after therapy has ended. In both men and women, serologic testing for syphilis should be done at the time of diagnosis of gonorrhea; thereafter, the serologic test for syphilis should be repeated monthly for four months. If results of serologic tests remain negative, no additional therapy is indicated. Positive serology for syphilis demands full treatment for this condition.

Nonspecific Urethritis

Next to gonococcal urethritis, the most commonly seen type of urethritis in men is the so-called nonspecific (nongonococcal) urethritis, NSU. Years ago this form of urethritis was termed nonspecific urethritis because routine bacteriologic cultures uniformly failed to show a pathogenic organism as the etiologic agent. In 1954 Shepard[5] isolated T-strain Mycoplasma organisms in men with nonspecific (or nongonococcal) urethritis; in 1964 Shepard[6] reported that T-strain Mycoplasma was the apparent etiological agent in cases of nonspecific urethritis in men. Since then, others[7-9] have reported T-strain Mycoplasma as a likely pathogen in cases of nonspecific urethritis.

In 1966 Furness and Csonka[10] initially isolated corynebacteria from the urethras of men with nonspecific (nongonococcal) urethritis. Later, in 1971, Furness and associates[11] reported that some cases of nonspecific urethritis were apparently due to corynebacteria.

Chlamydia was first isolated from the male urethra by Jones and associates[12] in 1964. Since

then Chlamydia has been isolated from patients with nonspecific urethritis or postgonococcal urethritis.[13-19] Oriel and co-workers[20] recovered Chlamydia from 36 percent of 98 men who experienced their first attack of nonspecific urethritis, but no isolates from urethral specimens from 34 men without urethritis. Similar results were obtained by Richmond and associates,[21] who obtained the organism in 36 percent of their patients with nongonococcal urethritis but from only 6 percent of controls. Evidence has also been obtained for the sexual transmission of Chlamydia.[20,22]

Thus, it appears that nonspecific urethritis can be due to T-strain Mycoplasma, corynebacteria, or Chlamydia organisms. Because special laboratory methods that are complicated and expensive are necessary to isolate any one of these three pathogens, it is often not practical for a practicing physician to attempt to specifically identify the pathogen in a given patient who has nongonococcal urethritis or urethritis that is not due to a bacterial organism that can be identified by routine bacteriologic culture techniques.

Diagnosis

A man who has nonspecific urethritis usually presents with a urethral discharge that is not purulent but is usually whitish or clear and mucoid. Often there will be associated burning on urination and there may be a red and edematous urethral meatus. Smears and cultures of the discharge should always be done to rule out gonorrhea, as well as cultures for routine bacterial pathogens. Assuming that findings on these smears and cultures are negative, and that trichomonads are not seen in a saline wet-mount of the discharge or in the first voided 5 to 10 ml of urine, a physician can be fairly sure that he is dealing with nonspecific urethritis.

It is helpful to centrifuge the first voided 5 to 10 ml of urine, as well as a late midstream aliquot of urine, and to look at the spun sediment under a microscope. In cases of urethritis, the first voided sediment will characteristically show an abnormally high number of pus cells, while the midstream urine will usually be normal. This clearly suggests inflammation in the urethra. Therefore, the diagnosis of nonspecific urethritis rests upon the demonstration of urethral inflammation, and the exclusion of other forms of specific urethritis (gonococcal, specific bacterial or trichomonal), unless the physician has access to a laboratory in which cultures for T-strain Mycoplasma, corynebacteria and Chlamydia organisms can be done.

Treatment

The treatment of choice for nonspecific urethritis, whether the infecting organism is T-strain mycoplasma, corynebacteria or Chlamydia is administration of tetracycline. Since the recurrence rate is fairly high when therapy is employed for only one week, a key to successful therapy is tetracycline to be taken for a minimum of two weeks continuously. If tetracycline cannot be used due to allergy, or if it proves to be ineffective, the second drug of choice is erythromycin.

The suggested treatment regimen is administration of tetracycline hydrochloride, 0.5 gram given orally four times a day for seven days, followed by 250 mg given orally four times a day for seven days; or, if tetracycline therapy proves ineffective, 0.5 gram of erythromycin given orally four times a day for seven days, followed by 250 mg given orally four times a day for seven days. Since transmission of the infective organism is frequently by means of sexual intercourse, recurrence of disease may represent reinfection, rather than relapse. In this case, the patient should be retreated with tetracycline and his sexual partner should be treated concurrently. In our experience orally given tetracycline is often less effective in treating women who have nonspecific vaginitis than it is in treating men with nonspecific urethritis. We have had more success in women by having them insert one vaginal tablet of oxytetracycline hydrochloride with polymyxin B sulfate (Terramycin® vaginal tablet) twice daily for 14 days. Both partners should abstain from sexual intercourse throughout the treatment period.

Specific Bacterial Urethritis

Bacterial urethritis due to a specific Gram-negative or Gram-positive bacterial pathogen is occasionally seen in men. The cause of the bacterial urethritis is usually secondary to an indwelling urethral catheter or results from colonization of the urethra by pathogenic vaginal bacteria following sexual intercourse. In the latter case, the colonization may be transient, the patient may be asymptomatic and the colonization may clear spontaneously. A man who has definite urethritis with a specific bacterial pathogen, however, usually has burning on urination, with or

without a urethral discharge, and may have urinary frequency and urgency—especially if the posterior urethra is also involved.

Diagnosis is made by localization cultures of the first voided 5 to 10 ml of urine (urethral culture), a midstream aliquot (bladder culture), the expressed prostatic secretions by prostatic massage (prostatic culture) and the first voided 5 to 10 ml of urine immediately following prostatic massage (prostatic culture).[23] When the quantitative bacterial colony counts of the urethral culture significantly exceed those of the bladder and prostatic cultures, the diagnosis of bacterial urethritis is made.

In women, Stamey[24-26] has shown that the flora of the vaginal introitus and the urethra are essentially mirror images. He has further shown that normal women with no history of urinary tract infections are only transiently colonized on the vaginal vestibule and in the urethra with small numbers of pathogenic bacteria that rapidly disappear spontaneously without symptoms or therapy. Conversely, those women who suffer with recurrent bouts of urinary tract infection frequently carry large numbers of pathogenic bacteria for long periods of time on their vaginal vestibules and urethras. Indeed, one can predict the infective organism of the next bladder infection by culturing the vaginas and urethras of these women in between bouts of cystitis because colonization of these areas usually precedes the entrance of the bacteria into the bladder. Colonization of the vagina and urethra with pathogenic bacteria (despite sterile bladder urine) can cause symptoms in women that exactly mimic those of cystitis (dysuria, urinary frequency and urgency, nocturia, and suprapubic and low back pain).

The diagnosis of vaginal colonization and bacterial urethritis in women is best established by means of localization cultures: culture of the external vaginal introitus, the first voided 5 to 10 ml of urine taken by a nurse with the patient in the lithotomy position on the table and culture of the midstream urine.[24] When the midstream urine culture is negative and the vaginal and urethral cultures are positive for pathogenic bacteria, the diagnosis of vaginal colonization and bacterial urethritis is established.

Treatment

In both men and women the treatment should be based upon the results of culture and sensitivity testing of the pathogen. An appropriate antibacterial agent should be selected and the patient should be treated with full dosage for seven to ten days. In women most antibacterial agents fail to clear the bacteria from the vagina or periurethral glands because these agents do not diffuse from plasma into the vaginal secretions or into the periurethral glands. The best drug for use in women is trimethoprim-sulfamethoxazole (Septra®, Bactrim™). Trimethoprim not only diffuses into vaginal secretions, but it is actually concentrated there several times the level in the plasma.[27] Indeed in most women, one can keep the vaginal introitus and the urethra free from virtually all pathogenic bacteria throughout continuous therapy with only a half tablet of trimethoprim-sulfamethoxazole taken each night at bedtime.

Urethritis Due to Trichomonads

Vaginitis due to Trichomonas vaginalis is a fairly common affliction of women. In such patients there usually are watery vaginal discharge and vaginal itching or burning, and often pain associated with sexual intercourse. If the organisms also invade the urethra, there also may be urinary symptoms of burning on urination, dysuria, urinary frequency and urgency, and nocturia. In chronic cases of vaginitis due to Trichomonas vaginalis the woman may be essentially asymptomatic, except for some vaginal discharge.

The urethra of a male sexual partner of a woman who has a vaginitis due to trichomonads may well be colonized with the organism, even though no symptoms may be seen. Therefore, to assure cure when the diagnosis is made in one partner of a couple, both partners should be treated concurrently to prevent reinfection. Men who are symptomatic from urethritis due to Trichomonas vaginalis usually have a whitish or clear urethral discharge, urinary burning, and often urinary urgency and frequency.

Diagnosis

In men, a saline wet-mount preparation of the urethral discharge will usually show the organisms under the high-dry power of the microscope. If the patient does not have a frank discharge, microscopic examination of the first voided 5 to 10 ml of urine will usually suffice to identify the organisms. To be certain of the diagnosis, one should see motile organisms and clearly identify the waving flagella. In some cases it may be necessary to culture the urethral discharge of the first voided 5 to 10 ml of urine on Kupferberg

medium, with the addition of 5 percent human serum and antibiotic (chloramphenicol, 1 mg per ml of medium).[28]

In women, the diagnosis of infection with this organism is usually readily made with a saline wet-mount of the vaginal discharge, as described above. To make the diagnosis of urethritis in women is difficult because of vaginal contamination. The diagnosis of female urethritis due to this organism is usually based upon clinical symptomatology because one rarely finds urethritis without an accompanying vaginitis. Cultures of the vaginal secretions or urethral swabs may occasionally be necessary to establish the diagnosis.

Treatment

In men, a 250 mg tablet of metronidazole (Flagyl®) should be given orally two or three times a day for ten days.

In women, a 250 mg tablet of metronidazole should be given orally three times a day for ten days. Or a 250 mg tablet of metronidazole may be given orally twice a day for ten days plus one 500 mg vaginal tablet of metronidazole inserted high into the vaginal cavity once a day for ten days. The vaginal tablets of metronidazole should not be used as the sole therapy.

In both men and women, sexual partners should be treated concurrently.

Comment

Several different types of infectious urethritis occur in both men and women. Effective therapy varies widely, depending upon the type of urethritis with which one is dealing. Recognition of the correct diagnosis by means of appropriate laboratory tests and the use of appropriate drug therapy for the specific type of urethritis will result in effective treatment.

REFERENCES

1. Johnson TW: Gonorrhea, *In* Hoeprich PD (Ed): Infectious Diseases. New York, Harper & Row, 1972, p 533

2. Peacock WL, Welch BG, Martin JE Jr, et al: Fluorescent antibody technique for identification of presumptively positive gonococcal cultures. Public Health Rep 83:337-339, 1968

3. Venereal Diseases Branch, State and Community Services Division, Center For Disease Control, Atlanta, Georgia: Recommended treatment schedules for gonorrhea. Ann Intern Med 76: 991, 1972

4. Austin TW, Brooks GF, Bethel M, et al: Trimethoprim-sulfamethoxazole in the treatment of gonococcal urethritis: Clinical and laboratory correlates. J Infect Dis 128 suppl:S666-S672, 1973

5. Shepard MC: The recovery of pleuropneumonia-like organisms from Negro men with and without nongonococcal urethritis. Am J Syph 38:113-124, 1954

6. Shepard MC, Alexander CE Jr, Lunceford CD, et al: Possible role of T-strain Mycoplasma in nongonococcal urethritis—A sixth venereal disease? JAMA 188:729-735, 1964

7. Csonka GW, Williams RE, Corse J: T-strain mycoplasma in non-gonococcal urethritis. Lancet 1:1292-1295, 1966

8. Ingham HR, MacFarlane WV, Hale JH, et al: Controlled study of the prevalence of T strain mycoplasma in males with non-gonococcal urethritis. Br J Vener Dis 42:269-271, 1966

9. Williams REO, Csonka GW, Corse J: Mycoplasma in the male genital tract, *In* Stamey TA, Hinman F Jr, Sanford JP (Eds): Urinary Infections in the Male—Proceedings of a Workshop. Washington, D.C., National Research Council, National Academy of Sciences, 1967, pp 117-126

10. Furness G, Csonka GW: Isolation of diphtheroids from non-gonococcal urethritis. Br J Vener Dis 42:185-190, Sep 1966

11. Furness G, Kamat MH, Kaminski Z, et al: Isolation of corynebacteria from non-specific urethritis. J Urol 106:557-561, 1971

12. Jones BR, Al-Hussaini MK, Dunlop EMC: Genital infection in association with TRIC virus infection of the eye—I. Isolation of virus from urethra, cervix, and eye: Preliminary report. Br J Vener Dis 40:19-24, 1964

13. Dunlop EMC, Al-Hussaini MK, Garland JA, et al: Infection of the urethra by TRIC agent in men presenting because of "non-specific" urethritis. Lancet 1:1125-1128, 1965

14. Dunlop EMC, Hare MJ, Darougar S, et al: Detection of Chlamydia (Bedsonia) in certain infections in man—II. Clinical study of genital tract, eye, rectum, and other sites of recovery of Chlamydia. J Infect Dis 120:463-470, 1969

15. Dunlop EMC, Hare MJ, Darougar S, et al: Chlamydial infection of the urethra in men presenting because of "non-specific" urethritis. Excerpta Medica International Congress Series No. 223, 1970, pp 494-500

16. Philip RN, Hill DA, Greaves AB, et al: Study of chlamydiae in patients with lymphogranuloma venereum and urethritis attending a venereal diseases clinic. Br J Vener Dis 47:114-121, 1971

17. Gordon FB, Quan AL: Isolation of Chlamydia trachomatis from the human genital tract by cell culture—A summary. Excerpta Medica International Congress Series No. 223, 1970, pp 476-484

18. Smith TF, Weed LA, Segura JW, et al: Isolation of *Chlamydia* from patients with urethritis. Mayo Clin Proc 50: 105-110, 1975.

19. Schachter J, Hanna L, Hill EC, et al: Are chlamydial infections the most prevalent venereal disease? JAMA 231:1252-1255, 1975

20. Oriel JD, Reeve P, Powis P, et al: Chlamydial infection: Isolation of *Chlamydia* from patients with non-specific genital infection. Br J Vener Dis 48:429-436, 1972

21. Richmond SJ, Hilton AL, Clarke SKR: Chlamydial infection: Role of *Chlamydia* subgroup A in non-gonococcal and post-gonococcal urethritis. Br J Vener Dis 48:437-444, 1972

22. Hilton AL, Richmond SJ, Milne JD, et al: *Chlamydia* A in the female genital tract. Br J Vener Dis 50:1-10, 1974

23. Meares EM Jr. Stamey TA: Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 5:492-518, 1968

24. Stamey TA: Urinary Infections. Baltimore, The Williams & Wilkins Co., 1972

25. Stamey TA: The role of introital Enterobacteria in recurrent urinary infections. J Urol 109:467-472, 1973

26. Stamey TA, Sexton CC: The role of vaginal colonization with Enterobacteriaceae in recurrent urinary infections. J Urol 113:214-217, 1975

27. Stamey TA, Condy M: The diffusion and concentration of trimethoprim in human vaginal fluid. J Infect Dis 131:261-266, 1975

28. Bailey WR, Scott EG: Diagnostic Microbiology, 3rd Ed. St. Louis, The C. V. Mosby Company, 1970, p 85

Refer to: Reza MJ, Young RT, Van Herle AJ, et al: Multiple endocrine adenomatosis type II (Sipple's syndrome) in twins. West J Med 123:441-446, Dec 1975

Multiple Endocrine Adenomatosis Type II (Sipple's Syndrome) in Twins

MICHAEL J. REZA, MD; ROY T. YOUNG, MD; ANDRE J. VAN HERLE, MD; VINCENT DeQUATTRO, MD; HAROLD S. COLE, MD, *and* JOSIAH BROWN, MD, *Los Angeles*

Medullary carcinoma of the thyroid, pheochromocytoma and multiple mucosal neuromas (MEA-II), a familial disorder of neuroectodermal tissue, is believed to be inherited in an autosomal dominant pattern. The occurrence of this syndrome in twins has not previously been reported. We have documented the presence of MEA-II in a pair of twins. The high incidence of bilaterality of pheochromocytoma is emphasized, as well as the usefulness of preoperative catecholamine fractionation, and vena cava catheterization sampling.

MULTIPLE ENDOCRINE ADENOMATOSIS TYPE II (MEA-II), often referred to as Sipple's syndrome, is a familial disorder of neuroectodermal tissue.[1,2] Clinical manifestations include medullary carcinoma of the thyroid, pheochromocytomas, mucosal neuromas and parathyroid adenomas or hyperplasia. This syndrome is felt to be an autosomal dominant trait with a high degree of penetrance.[1] To our knowledge, the syndrome has not been described in either monozygotic or dizygotic twins. A set of twins with characteristic features of this syndrome is the subject of the present report.

Reports of Cases

CASE 1. A 19-year-old unmarried woman was referred to the University of California, Los Angeles, School of Medicine in March of 1968 for evaluation of severe headaches which had been occurring for six months. These episodic headaches were associated with pronounced flushing, weakness and tremor. The patient was evaluated at another hospital in November of 1967 where results of screening tests for pheochromocytoma were reportedly normal. An enlarged thyroid was noted and when a total thyroidectomy was done, medullary carcinoma with amyloid stroma was found to be present. In 1967 a thyroidectomy had been carried out in the patient's twin sister with the same findings. In both sisters, total dental extraction was done in 1967 for what was termed "soft, chalky teeth." The father's whereabouts were vague; however, he was not known to have any medical problems. The mother, at age 51, had no known medical problems. A 22-year-old sister appeared healthy.

On physical examination the patient was seen to have a peculiar facies with a rather narrow jaw, and multiple raised neuromas on the tongue. Prominent pes cavus was present. The blood pressure was 110/70 mm of mercury. The pulse rate was 80 beats per minute. Right cervical adenopathy was noted on examination of the neck. In the remainder of the physical examination, findings were within normal limits.

From the Department of Medicine, Division of Endocrinology, University of California, Los Angeles, School of Medicine (Drs. Reza, Young, Van Herle, Cole and Brown); and the Department of Medicine, White Memorial Hospital, Loma Linda University, Los Angeles (Dr. DeQuattro).

Submitted, revised, May 8, 1975.

Reprint requests to: Michael Reza, MD, Department of Medicine, University of California, Los Angeles, School of Medicine, 10833 LeConte Avenue, Los Angeles, CA 90024.

ABBREVIATIONS USED IN TEXT

MEA-II = multiple endocrine adenomatosis
IVC-T_{12} = the inferior vena cava sample obtained at the level of the 12th thoracic vertebra

An oral glucose tolerance test gave the following values: fasting, 90 mg per 100 ml; 60 minutes, 164 mg per 100 ml; 90 minutes, 148 mg per 100 ml; 120 minutes, 234 mg per 100 ml; and 180 minutes, 120 mg per 100 ml. Findings on studies of serum calcium, phosphorus, creatinine, electrolytes and plasma volume, as well as on a complete blood count, x-ray study of the chest and electrocardiogram, were within normal limits. A karyotype was 46 XX. Results on 24-hour urine samples disclosed elevated vanillylmandelic acid at 9.8 mg in 24 hours (normal 0.7 to 6.8 mg in 24 hours) and total catecholamines of 210 μg in 24 hours (normal 15 to 140 μg in 24 hours). Forty-two percent of the catecholamines were epinephrine. A histamine stimulation test, using 50 μg of histamine base, gave positive findings. The blood pressure rose from 120/80 to 250/160 mm of mercury two minutes after injection and the patient became severely symptomatic. Alpha blockade was started using phenoxybenzamine (Dibenzyline®), 10 mg given four times a day for ten days before surgical operation.

Anesthetic induction was uneventful. Manipulation of the left adrenal resulted in pronounced hypertension and frequent premature ventricular contractions. Manipulation of the right adrenal, which felt normal to palpation, did not elicit cardiovascular changes. A left adrenalectomy was carried out, as well as incidental appendectomy.

On pathologic examination the left adrenal gland weighed 36 grams and contained a well-encapsulated pheochromocytoma. The appendix showed bizarre, enlarged ganglioneuronal elements in the submucosa, consistent with ganglioneuromatosis. The patient's family refused to enter the hospital for screening tests, and the patient was lost to follow-up.

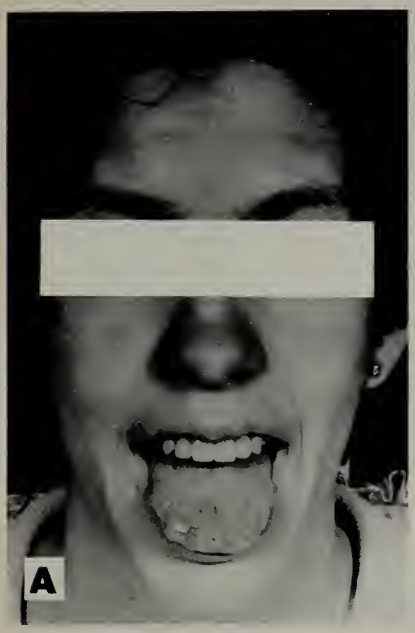
CASE 2. The twin sister of the patient described above was referred to the University in August of 1970 at age 21 after experiencing two brief episodes of headaches and flushing similar to those her sister had before removal of the pheochromocytoma. Both of these twins were raised together in the same family until age 18. She related a history of surgical operation for a right thyroid nodule which on pathologic examination was consistent with a medullary carcinoma. Subsequently total thyroidectomy had been done.

On physical examination, the patient's appearance was identical to that of her sister (Figure 1A). The patient was edentulous; a high-arched palate and multiple neuromas of the tongue were present (Figure 1B and Figure 1C). Pes cavus was also present. The blood pressure on admission was 110/50 mm of mercury. The pulse rate was 75 beats per minute.

Findings on an x-ray film of the chest, electrocardiogram, urinalysis, complete blood count and determinations of plasma volume, calcium, phosphorus, creatinine, electrolytes, fasting glucose, plasma cortisol (7 am), plasma follicle-stimulating hormone and luteinizing hormone were all within normal limits. A karyotype was 46 XX. Urinary vanillylmandelic acid was 141 μg per hour (normal 234 ± 108 μg per hour) and total urinary catecholamine excretion was 1.5 μg per hour (normal 2.6 ± 1.3 μg per hour) of which 33 percent was epinephrine.

Result of a histamine test using 50 μg of histamine base was considered positive. The blood pressure rose from 120/70 to 180/100 mm of mercury three minutes after injection and the patient became severely symptomatic. Two-hour timed urinary catecholamine studies, with samples collected immediately preceding histamine injection and for two hours following histamine injection showed a diagnostic rise in urinary catecholamines (Figure 2). On adrenal venography, an enlarged, distorted right adrenal gland was noted. Adrenal vein effluents subjected to norepinephrine and epinephrine measurements showed normal adrenal vein values bilaterally, both in absolute values and relative percentage of epinephrine (74 percent for the right adrenal and 83 percent for the left adrenal) (Table 1). These values were consistent with the percent of epinephrine found in normal adrenal tissue (Table 2). The inferior vena cava sample obtained at the level of the 12th thoracic vertebra (IVC-T_{12}) was clearly abnormal both in absolute value and in percent of epinephrine (46 percent). This percentage of epinephrine was also found in the tumor (49 percent) (Table 2, site 2) and in the urine after histamine injection (45 percent) (Figure 2).

With this high degree of suspicion, therapy with both phenoxybenzamine and propranolol was started and surgical exploration was undertaken. The left adrenal was felt to be normal. No increase in blood pressure occurred with massage



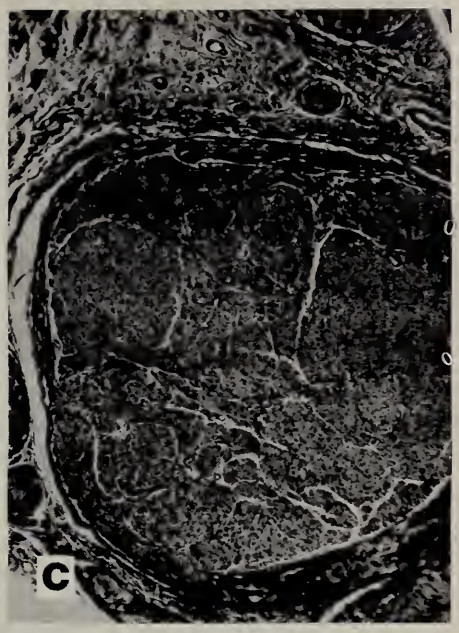


Figure 1.—A, photograph of patient (Case 2) showing facies typical of many patients with MEA-II syndrome. Neuromas are evident on the tongue. **B,** close-up view of the tongue of a similar patient with MEA-II syndrome showing numerous pale, glistening neuromas. **C,** histological section of a mucosal neuroma of the tongue from Case 2 showing plexiform bundles of nerve tissue (hemotoxylin-eosin stain, reduced from 84×).

of the left adrenal. The right adrenal gland was enlarged and was resected. The gland weighed 18 grams (Figure 3) and two separate pheochromocytomas were noted when it was cut. Catecholamine levels in extracts of both tumors and surrounding normal adrenal tissue are summarized in Table 2. Subsequent to operation no further episodes of headaches occurred.

In February of 1971, bilateral radical neck surgical procedures were carried out for metastatic

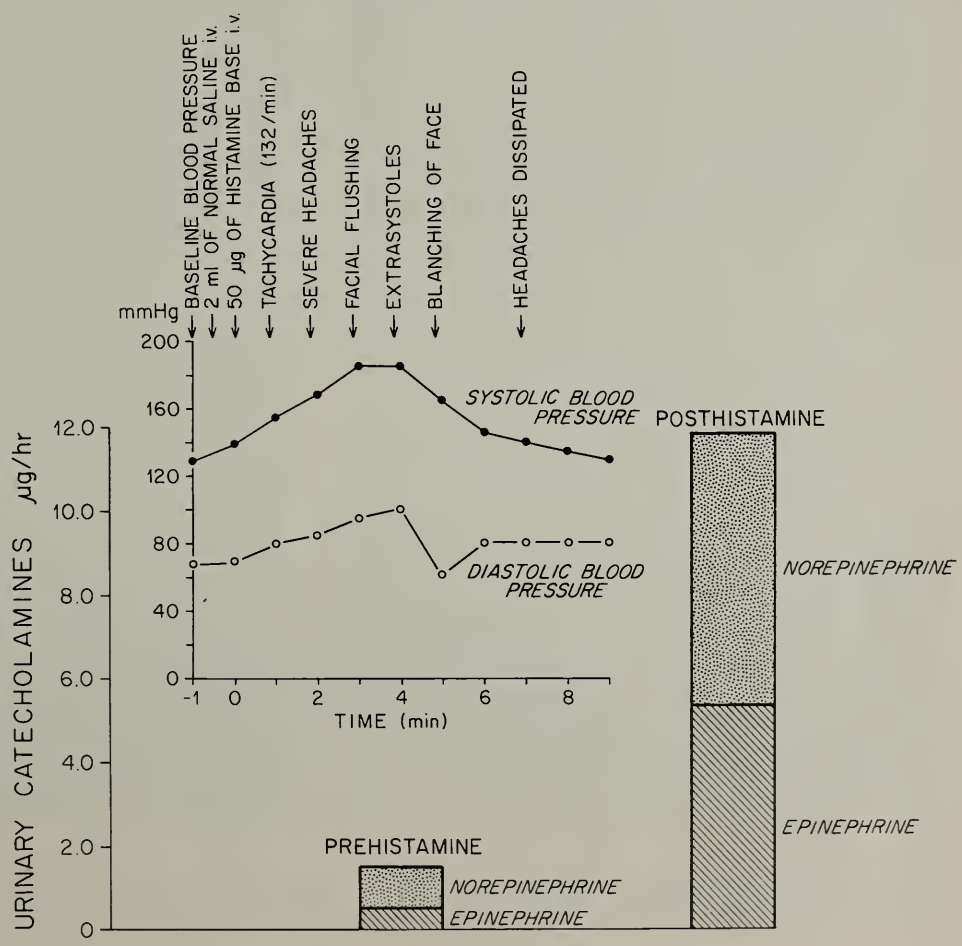


Figure 2.—Histamine stimulation test in Case 2, showing the effect of histamine on urinary catecholamine excretion, as well as the temporal sequence of clinical symptomatology after histamine injection.

medullary thyroid carcinoma. While the patient was recovering from this intervention, the sudden onset of respiratory obstructive symptoms occurred followed by cardiac arrest. Resuscitative measures were unsuccessful. At autopsy, the presence of additional pheochromocytomas in the remaining left adrenal as well as the organ of Zuckerkandl were found. Diffuse intestinal ganglioneuromatosis was also present (Figures 4A and 4B).

Since HL-A typing was not available at the time these observations were made, there is no proof that the two patients discussed here were monozygotic twins although their identical appearance strongly indicated such a relationship.

Discussion

The syndrome of medullary carcinoma of the thyroid with associated findings of pheochromocytoma, multiple mucosal neuromas, parathyroid adenomas or hyperplasia has been well documented in the literature in recent years.[2-5] Melvin and co-workers[6] have carefully studied 89 members of an afflicted kinship (J Family) and concluded that this syndrome is due to an autosomal dominant gene. The reported cases of affected siblings or parent and offspring in several families, support this conclusion.[7,8] The present cases are unique in that they appear to be the first reported cases of MEA-II syndrome in twins. It is unfortunate that despite repeated attempts, we were not able to maintain follow-up with the first patient.

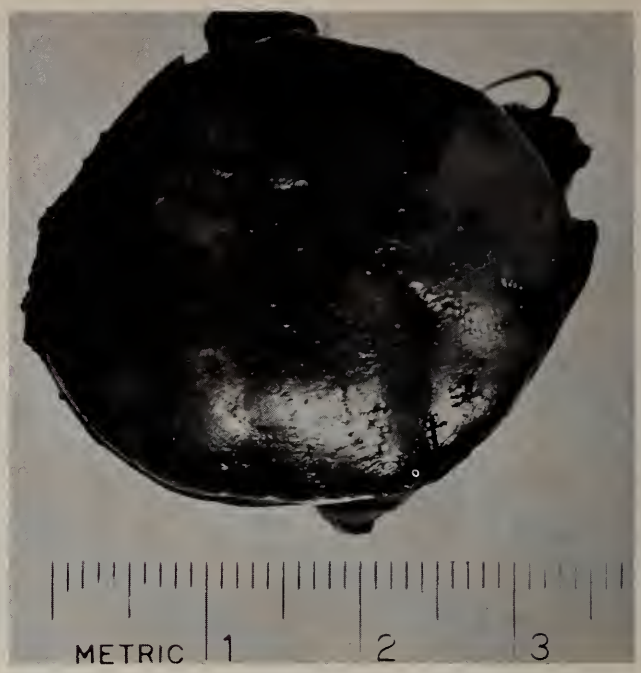


Figure 3.—Enlarged adrenal gland removed at surgical operation in Case 2. On sectioning, two pheochromocytomas were found within the gland.

An interesting component of this syndrome is the generalized intestinal ganglioneuromatosis (Figure 4). Inspection of the tongue or examination of appendices or other intestinal tissue removed during surgical procedures on the abdomen may indeed provide an early clue to the diagnosis in asymptomatic patients. The neuromas are made up of bundles of enlarged nerves which have a plexiform appearance. Presumably abnormalities of both endodermal and ectodermal tissue in this

TABLE 1.—*Plasma Norepinephrine and Epinephrine (ng/liter) in Case 2*

Site	*Norepinephrine (NE)*	*Epinephrine (E)*	*NE+E**	*Percent E*
Inferior vena cava at 5th lumbar vertebra	448	170	618	27.5
Inferior vena cava at 12th thoracic vertebra†	1,337	1,129	2,466	45.7
Interior vena cava at 11th thoracic vertebra	318	370	688	53.7
Left renal vein	479	172	651	26.4
Right renal vein	460	177	637	27.7
Left adrenal vein	4,292	20,640	24,932	82.7
Right adrenal vein	13,306	38,323	51,629	74.2

*Normal supine value in peripheral venous blood NE+E: 440±120 ng/liter.[11]
†These data suggest the presence of a right adrenal pheochromocytoma.

TABLE 2.—*Adrenal Tissue Catecholamines (μg/gram/wet weight of tissue)*

Site	*Norepinephrine (NE)*	*Epinephrine (E)*	*NE+E*	*Percent E*
Tumor - 1	4,387	1,011	5,398	18.72
Tumor - 2	2,331	2,248	4,579	49.1
Normal adrenal tissue	428	1,092	1,520	71.8

Catecholamine levels in adrenal tissue obtained from Case 2. Tumor sites 1 and 2 are of two separate pheochromocytomas within that gland. Note the percent of epinephrine in normal and tumor tissue.

syndrome reflects a genetically determined defect in the embryonic neuroectodermal stem cell stage.

The thyroid tumor is most often bilateral,[6] as in our patients, and consequently total thyroidectomy should always be done. Circulating levels of thyrocalcitonin are usually increased, as shown by Melvin and co-workers,[6] and can be a valuable marker in detecting preclinical disease. At the time our patients presented, thyrocalcitonin measurements were unavailable to us. As shown by the data of Tashjian and associates, all family members of a patient with MEA-II should be given a complete examination including determinations of serum calcitonin levels and serum parathyroid hormone levels, and screening tests to exclude the presence of a pheochromocytoma.

In the MEA-II syndrome, pheochromocytomas are most often bilateral. Sarosi[3] concluded that in 77 percent of patients with familial medullary carcinoma and pheochromocytoma, the pheochromocytoma is bilateral. If parathyroid adenomas are present, the incidence of pheochromocytomas has been reported to be as high as 84 percent.[3] In Case 2, the patient ultimately was found to have bilateral pheochromocytomas at autopsy even though results of careful adrenal and para-aortic examination were negative at the time of surgical operation. It would appear, then, that in patients with this syndrome the probability of a bilateral pheochromocytoma is high. When unilateral pheochromocytoma is found in patients with this syndrome, should bilateral adrenalectomy also be carried out? The risk of a second operation and recurrent functioning pheochromocytoma would have to be weighed against lifelong adrenal replacement therapy in any given patient. We would only recommend that physicians be aware of this high incidence of bilaterality.

The plasma catecholamine studies in the inferior vena cava done in Case 2 indicate the usefulness and limitations of this technique in the localization of pheochromocytomas. In Table 1 both the right and left adrenal vein catecholamine levels are normal; that is, the proportion of epinephrine is normal for adrenal venous blood (74

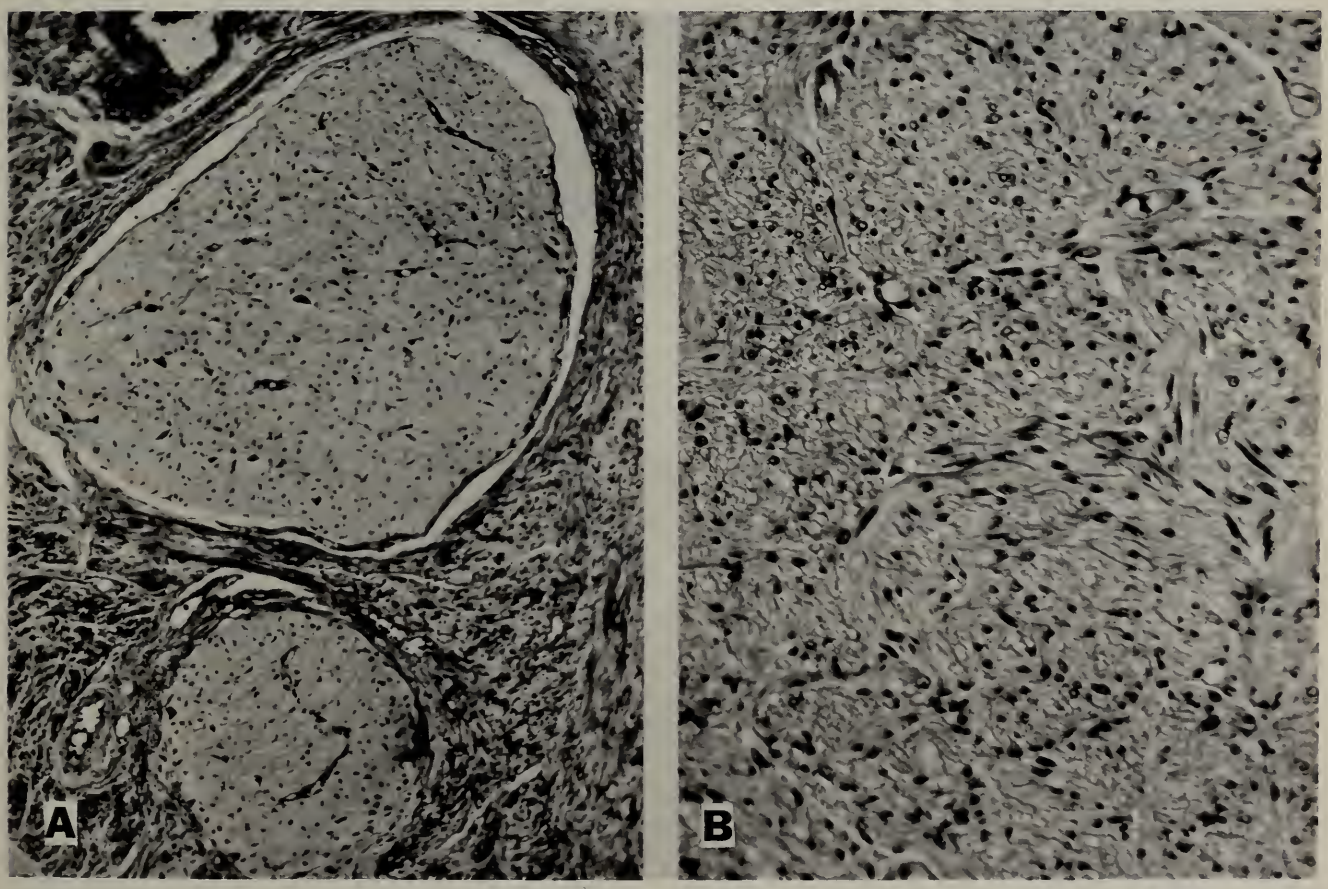


Figure 4—A, section of appendix in Case 2 showing large irregular conglomerations of nerve fibers and ganglion cells within the muscular coat (hematoxylin eosin stain magnification 85×). **B,** high-power view of the smaller neuroma seen in Figure 4A showing interlacing bands of nerve fibers arranged in parallel strands (hematoxylin eosin stain magnification 350×).

percent and 83 percent epinephrine). Also, the magnitude of these levels are within the range determined for normal adrenal vein plasma. However, the IVC-T_{12} sample (Table 1) which would be at the level of the right adrenal gland, is clearly abnormal both in proportion and magnitude of epinephrine and norepinephrine in vena cava blood. These data strongly favored the presence of a tumor in the origin of the right adrenal gland. Indeed, the percentage of epinephrine (46 percent) found at the IVC-T_{12} level was quite similar to the percentage (49 percent) found in site 2 of the subsequently removed right adrenal tumor, and that found in the urine (45 percent) after the histamine test (Figure 2). Therefore, one can strongly suspect the presence of pheochromocytoma even when adrenal vein catecholamine levels are normal.

On the other hand, the data in Table 1 failed to indicate the presence of a left adrenal tumor. Yet, on subsequent postmortem examination a pheochromocytoma of the left adrenal gland was found. It appears, therefore, that the diagnosis of and the actual localization of a tumor by vena cava catheterization sampling depends on a number of factors: (1) The time the sample is obtained relative to the time the tumor is secreting catecholamine; (2) the anatomic drainage of the adrenal vein or tumor veins into the vena cava or the renal or hepatic veins (the right adrenal vein usually drains medially into the vena cava; the left adrenal vein usually drains into the left renal vein, and may be joined with the inferior phrenic vein); (3) The location of the catheter tip when the blood is withdrawn; (4) The intake of drugs such as alpha-methyldopa or L-dopa, which interfere in the assay system.

In addition, in the present case (Table 2) it is conceivable that the left pheochromocytoma had not yet reached a mass sufficient to cause elevation of circulating catecholamines at the time the vena cava study was done. The fact that the manipulation of the left adrenal during the first operation did not cause any cardiovascular changes supports this speculation. While a step-up in concentration of catecholamines in the vena cava is helpful in the location of the tumor site, negative evidence does not seem to rule out the presence of such a tumor.

Case 2 also exemplifies the usefulness of provocative testing for pheochromocytoma in a patient at high risk but in whom baseline urinary values for catecholamines and their metabolites are normal (Figure 2). As can be seen, collection of urine for catecholamines immediately following the histamine stimulation test can be a valuable aid in the diagnosis of pheochromocytoma. In addition fractionation of catecholamines before surgical operation may be helpful in localizing the pheochromocytomas, since with rare exception a high proportion of epinephrine indicates an intra-abdominal tumor, most commonly in the adrenal gland.[9,10]

REFERENCES

1. Melvin KEW, Tashjian AH Jr, Miller HH: Studies in familial (medullary) thyroid carcinoma. Prog Horm Res 28:399-470, 1972
2. Ljungberg O, Cederquist E, von Studnitz W: Medullary thyroid carcinoma and phaeochromocytoma—A familial chromaffinomatosis. Br Med J 1:279-281, 1967
3. Sarosi G, Doe RP: Familial occurrence of parathyroid adenomas, pheochromocytoma, and medullary carcinoma of the thyroid with amyloid stroma (Sipple's syndrome). Ann Intern Med 68:1305-1309, 1968
4. Ruppert RD, Buerger LF, Chang WWL: Pheochromocytoma, neurofibromatosis and thyroid carcinoma. Metabolism 15: 537-541, 1966
5. Gorlin RJ, Sedano HO, Vickers RA, et al: Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid—A syndrome. Cancer 22:293-299, 1968
6. Melvin KEW, Miller HH, Tashjian AH Jr: Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. N Engl J Med 285:1115-1120, 1971
7. Li FP, Melvin KEW, Tashjian AH Jr, et al: Familial medullary thyroid carcinoma and pheochromocytoma—Epidemiologic investigations. J Natl Cancer Inst 52:285-287, 1974
8. Keiser HR, Beaven MA, Doppman J, et al: Sipple's syndrome: Medullary thyroid carcinoma, pheochromocytoma and parathyroid disease. Ann Intern Med 78:561-579, 1973
9. Jaattela A: Catecholamines in the diagnosis and localization of phaeochromocytoma. Ann Clin Res 4:78-83, 1972
10. Crout RJ, Sjoerdsma A: Catecholamines in the localization of pheochromocytoma. Circulation 22:516-525, 1960
11. Engelman K, Portnoy B: A sensitive double-isotope derivative assay for norepinephrine and epinephrine—Normal resting human plasma levels. Circ Res 26:53-57, 1970

Refer to: Deftos LJ, Roos BA, Parthemore JG: Calcium and skeletal metabolism (Medical Progress). West J Med 123:447-458, Dec 1975

Calcium and Skeletal Metabolism

LEONARD J. DEFTOS, MD; BERNARD A. ROOS, MD, *and*
JACQUELINE G. PARTHEMORE, MD, *La Jolla*

DURING THE past several years many new discoveries have been made in the field of calcium and skeletal metabolism. These discoveries have been of both fundamental importance and clinical relevance. The general theme that has emerged from this new knowledge is that calcium and skeletal metabolism is regulated by a complex and dynamic interaction of three hormones—parathyroid hormone (PTH), calcitonin (CT) and vitamin D (Table 1). These hormones exert their biological effects on the three organ systems that maintain calcium and skeletal homeostasis—bone, kidney and the gastrointestinal tract. In turn, the secretion and metabolism of these three hormones are influenced by these organ systems and others, such as the skin and liver, and by the concentrations of bone minerals which circulate in peripheral plasma. Finally, the hormones interact to influence each other's secretion, biological effects and metabolism.[1] Several recent reviews have considered these advances in bone mineral metabolism.[2-9] In this article, we shall emphasize those developments which seem to have the most clinical importance for each of the calcitropic peptide hormones. The emerging hormonal role of vitamin D has been thoroughly considered in recent publications, including one in this journal.[7-9]

From the Department of Medicine (Endocrinology), University of California, San Diego, School of Medicine, and the Veterans Administration Hospital, San Diego.

Supported by grants from the National Institutes of Health (AM15888), The American Cancer Society (CI-80), and the Veterans Administration. (Dr. Deftos is a Clinical Investigator and Dr. Parthemore is a Research and Education Associate of the Veterans Administration.)

Reprint requests to: Leonard J. Deftos, MD, Veterans Administration Hospital, Room 3258, 3350 La Jolla Village Drive, San Diego, CA 92161.

Parathyroid Hormone

Biosynthesis, Secretion and Metabolism

The process by which parathyroid hormone is produced by the parathyroid gland and delivered to its target organs has been discovered to be increasingly complex. There is at least one, and perhaps more, biosynthetic precursor to the 84 amino acid peptide which is the main hormonal constituent of the parathyroid glands.[10-14] The precursor(s), or prohormone(s), is converted into native hormone within the gland and then secreted into the circulation. Once in the circulation, the 84 amino acid peptide is broken down in plasma or at tissues or both into smaller peptide fragments.[15] Under some circumstances, hormonal precursors, hormone and perhaps hormone fragments may be secreted directly into the circulation from the parathyroid glands.[11-16] Therefore, there exist in plasma multiple forms of parathyroid hormones. These species of hormone have varying biological and immunological activity.[1-3,15,16] The latter observation is of practical significance since clinical measurements of the hormone are made by immunoassay systems which can react variously with different species of the hormones. Therefore, different immunoassay systems may give different results when applied to clinical measurements. *This emphasizes the importance of being familiar with the characteristics of any immunoassay system which one is using for clinical decisions.* If this precaution is taken, the immunoassay for parathyroid hormone can be very useful in the differential diagnosis of dis-

percent
mag-
te

ABBREVIATIONS USED IN TEXT

CT = calcitonin
OAF = osteoclastic activation factor
PTH = parathyroid hormone

orders of calcium and skeletal homeostasis (Table 2).

Nonionic regulation of parathyroid hormone secretion. The importance of divalent cations, especially calcium, in the regulation of parathyroid hormone secretion is well-documented.[1] However, recent observations have suggested that other factors may also regulate hormonal secretion. A series of recent experiments has implicated other hormones, such as calcitonin and cortisol, and other organ systems, such as the gastrointestinal system and the central and peripheral nervous system (Figure 1), in the regulation of parathyroid hormone secretion.[17-20] Although many of these observations are preliminary and await further confirmation, their implications are of potential importance. They suggest that the control of parathyroid hormone secretion is more complex and multifactorial than previously appreciated.

Primary and Ectopic Hyperparathyroidism

Most patients with primary hyperparathyroidism have plasma levels of hormone which are absolutely or relatively (to blood calcium) elevated. By contrast, patients who have hypercalcemia not due to parathyroid gland neoplasia will have a suppressed parathyroid hormone level. However, it must be kept in mind that some nonparathyroid tumors are associated with excess parathyroid hormone production (pseudohyperparathyroidism, ectopic hyperparathyroidism).[1] Several controversies remain unresolved regarding the ectopic production of parathyroid hormone. How common is ectopic hyperparathyroidism in the differential diagnosis of hypercalcemia and is ectopically-produced PTH similar in molecular structure to glandular PTH?[21,22] The latter controversy is of obvious fundamental importance for molecular biology, but also important for clinical medicine. Some laboratories report that there are structural differences between

TABLE 2.—*Differential Diagnosis of Hypercalcemia*

Artifactual
- Hyperproteinemia
  - Venous stasis during blood collection
  - Hyperalbuminemia (e.g., hyperalimentation)
  - Hypergammaglobulinemia (e.g. myeloma)

Malignancy
- Solid tumors
- Hematological
  - Myeloma
  - Lymphoma
  - Leukemia

Endocrinological
- Primary hyperparathyroidism
  - Multiple endocrine adenomatoses, types I and II
- Inappropriate secondary hyperparathyroidism (renal failure)
- Hyperthyroidism
- Hypoadrenalism

Drugs
- Vitamin D intoxication
- Thiazides
- Calcium
  - Milk alkali syndrome
  - Dialysis

Granulomatous Disorders
- Sarcoidosis
- Tuberculosis
- Berylliosis

Pediatric Disorders
- Infantile hypercalcemia
- Hypophosphatasia

Immobilization
- Paget's disease
- Young patients

TABLE 1.—*Hormonal Regulation of Calcium and Skeletal Metabolism. The Effect of Each of the Calcitropic Hormones on Calcium (Ca^{++}) and Phosphate ($PO_4^{=}$) at the Three Critical Organ Systems and the Resulting Blood Concentrations Are Shown*

	Gastrointestinal Absorption		*Net Bone Mobilization*		*Renal Clearance*		*Blood Concentration*	
	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$	Ca^{++}	$PO_4^{=}$
PTH	I	I	I	I	D	I	I	D
CT	D	D	D	D	I	I	D	D
Vitamin D	I	I	D/I	D/I	D	D	I	I

CT = calcitonin
D = decreased
D = decreased, not firmly established
D/I = decreased or increased, not firmly established
I = increased
I = increased, not firmly established
PTH = parathyroid hormone

ectopic and glandular PTH and that these structural differences allow clinical distinctions to be made between ectopic and glandular PTH overproduction with radioimmunoassay and ancillary procedures.[21] Other laboratories have found only a small incidence of ectopic hyperparathyroidism in the differential diagnosis of the hypercalcemia of malignancy.[22] These laboratories emphasize that there may be other humoral factors associated with malignancy that resorb bone and produce hypercalcemia. Several such factors have been described in experimental studies. They include prostaglandins, osteoclastic activation factor (OAF) and other as yet uncharacterized substances.[23,24] The ultimate resolution of the etiological importance of parathyroid hormone and other bone resorbing factors in the hypercalcemia of malignancy will be of great clinical importance in diagnosis and management.

TABLE 3.—*Classification of Nephrolithiasis*

Normocalciuric
Hypercalciuric
Idiopathic
Resorptive
Absorptive
Calciuric

Nephrolithiasis

There has been increased understanding of the several pathogenetic mechanisms that can be involved in the development of calcium-containing renal stones (Table 3). This has resulted in more rational management of affected patients. The association of primary hyperparathyroidism with hypercalciuria and nephrolithiasis is well-known (resorptive hypercalciuria) and in these patients, treatment of the nephrolithiasis is surgical treatment of the hyperparathyroidism.[1] However, evi-

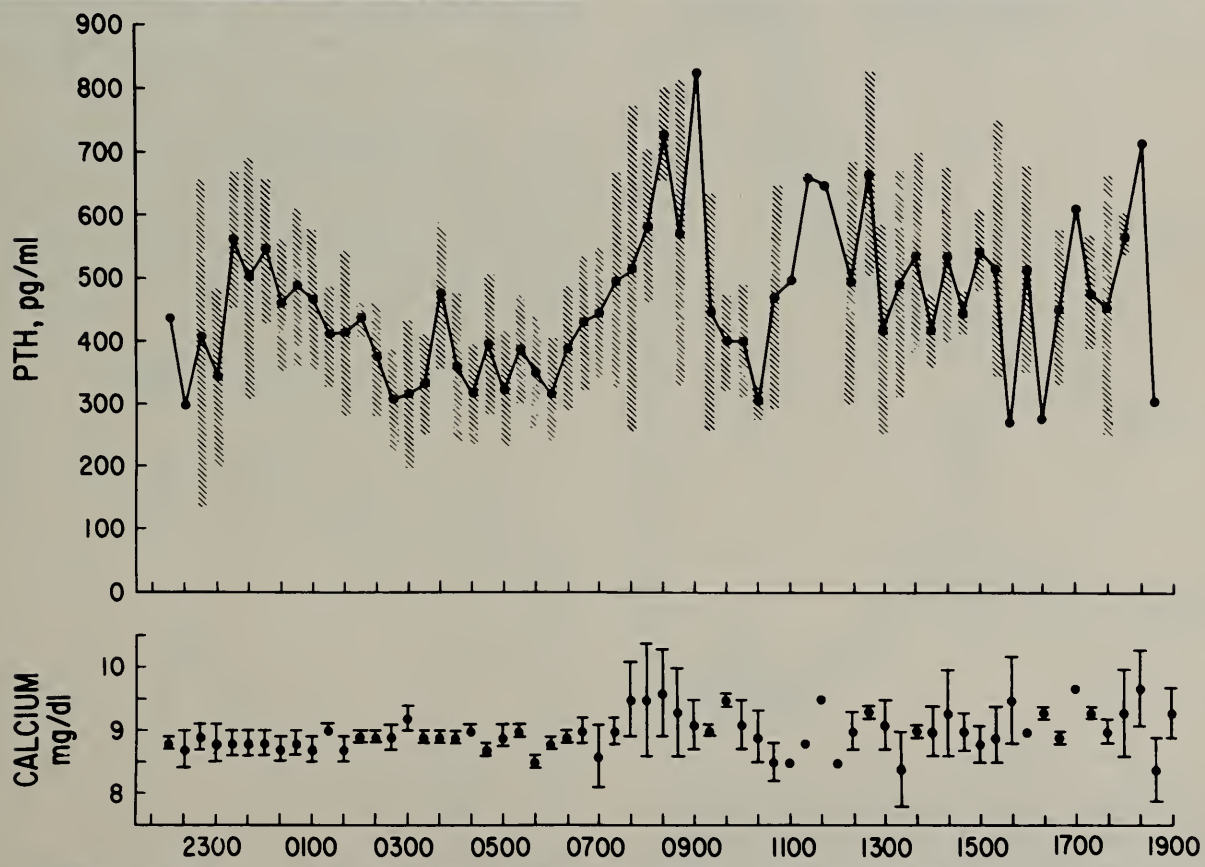


Figure 1.—Summary of the changes in plasma parathyroid hormone (PTH) and calcium in ten normal subjects obtained by frequent blood sampling through an indwelling catheter during continuous studies of up to 36 hours duration. The mean data were derived by dividing each hour into 20-minute segments and averaging the plasma PTH and calcium for each of the subjects during each of the 20-minute segments. Despite the fact that such data reduction tends to minimize and even obscure the changes seen in individual subjects it is evident that PTH concentrations, and less so calcium levels, change in an episodic or pulsatile manner. If the individual samples were normalized in a less arbitrary fashion and to a more relevant physiological measurement (such as, for example, electroencephalogram (EEG) changes during sleep), it is likely that a different pattern, but still pulsatile, would have resulted for PTH and calcium. The shaded areas and the bars represent the standard error for the indicated mean of each of the determinations.

dence has been presented recently to indicate that hyperparathyroidism in some patients with hypercalciuria may be a secondary rather than a primary phenomenon.[25] These patients have a primary renal hypercalciuria which results in calcium loss. To compensate for this loss, there is an increased secretion of parathyroid hormone which decreases the renal clearance of calcium. There is disagreement as to whether renal hypercalciuria and secondary hyperparathyroidism is a rare or common cause of nephrolithiasis and studies are in progress to establish the epidemiological significance of this disorder.[26] Controversies about incidence notwithstanding, the establishment of the presence of renal hypercalciuria for a given patient is therapeutically important. A patient with kidney stones who fits the diagnostic criteria established for renal hypercalciuria is a candidate for thiazide treatment since thiazides have been shown to decrease the renal calcium loss in such patients.[25]

Absorptive hypercalciuria is another clinical entity in the differential diagnosis of nephrolithiasis which has therapeutic significance. In contrast to a patient with primary hyperparathyroidism whose hypercalciuria results from the calcium release from bone by its increased resorption, the hypercalciuria in patients, usually males, with this form of nephrolithiasis results from the gastrointestinal absorption of an abnormal amount of dietary calcium (absorptive hypercalciuria).[27] Accordingly, in contrast to patients with renal hypercalciuria, rational treatment of these patients dictates a low-calcium diet.[28]

Despite this increased understanding of the pathogenesis of hypercalciuria and nephrolithiasis, many patients cannot be fit into the diagnostic categories of absorptive, resorptive or renal hy-

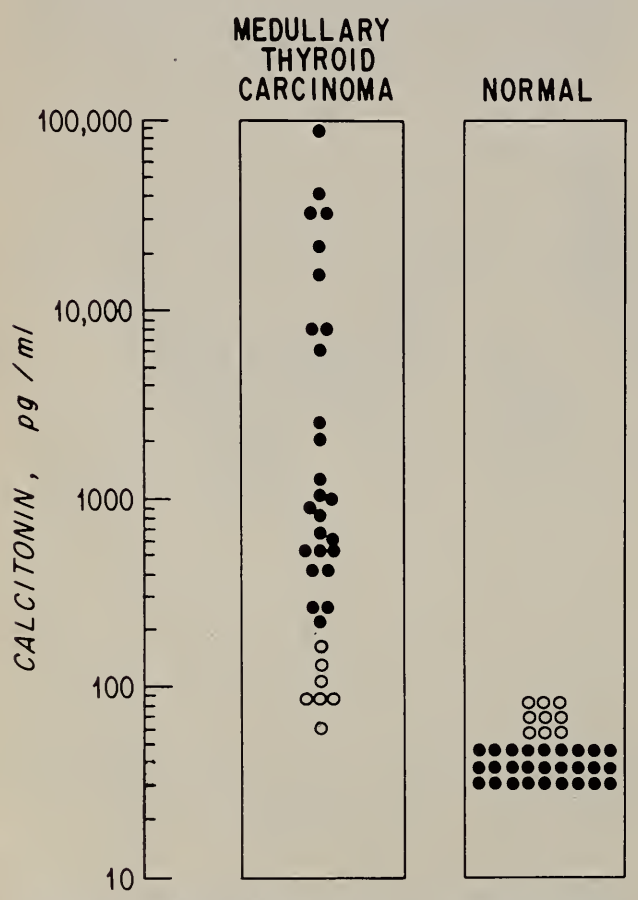


Figure 2.—Basal plasma calcitonin measurements in 33 subjects with histologically proved medullary thyroid carcinoma and in 36 normal subjects. At left (closed circles), patients with elevated basal concentrations of calcitonin; at right (closed circles), normal patients with undetectable concentrations of calcitonin. Some patients with thyroid tumors (open circles, at left) had basal calcitonin levels that could not be clearly distinguished from some normal subjects (open circles, at right). (Reproduced with permission from: Deftos LJ: Radio immunoassay for calcitonin in medullary thyroid carcinoma. JAMA 227:403-406, Jan 28, 1974. Copyright 1974, American Medical Association.)

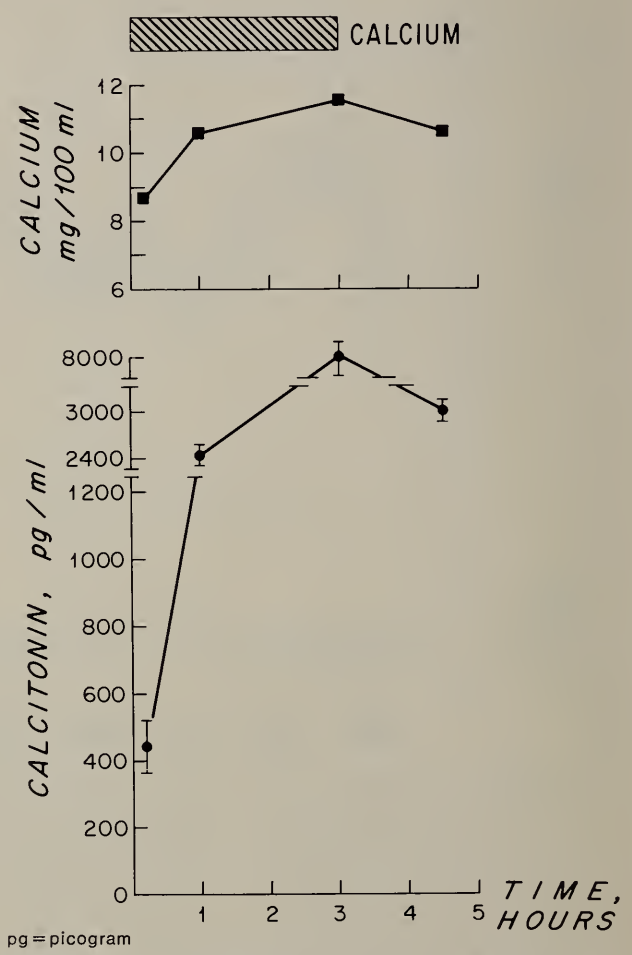


Figure 3.—Stimulatory effect of calcium (shaded area) infusion (12 mg per kg of body weight every three hours) on plasma calcitonin in a patient with medullary thyroid carcinoma (see Figures 4 and 5).

percalciuria.[1] Furthermore, many patients with calcium-containing renal stones do not have easily demonstrable hypercalciuria. Many of these previously-mentioned forms of therapy—dietary restriction of calcium, thiazide therapy, parathyroid surgical procedures—along with phosphate therapy, have been tried in such patients with varying degrees of success and newer forms of treatment are being introduced.[27,28] The intermittent nature of the nephrolithiasis makes it difficult to evaluate the effects of therapy. Although regimens that are apparently successful and do not harm the patient may be continued, a reasonably prudent regimen for all patients with hypercalciuria should include adequate hydration. The patients should be encouraged to drink as much (calcium-free) fluid as is manageable for them. Postprandial fluids are especially important and dehydration should be avoided.

Asymptomatic and Normocalcemic Hyperparathyroidism

The patient with the classical picture of hyperparathyroidism—significant hypercalcemia, bone symptoms, and osteitis fibrosa cystica and recurrent nephrolithiasis—is no longer commonly seen by physicians. Clinical and fundamental progress have greatly modified the clinical presentation of contemporary patients with hyperparathyroidism.[29] The progress has been in a better understanding of the gross as well as subtle manifestations of the illness and the greater availability of diagnostic procedures. A great impact has been made by the increased availability, especially as a part of screening procedures, of calcium determinations. More recently, direct PTH measurements by radioimmunoassay are now available to most physicians.[30] This progress has resulted in delineation of the syndromes of asymptomatic hyperparathyroidism and normocalcemic hyperparathyroidism. Close scrutinity shows that these appellations are probably misnomers for the large part, but they emphasize the evolution of the clinical presentation of primary hyperparathyroidism.

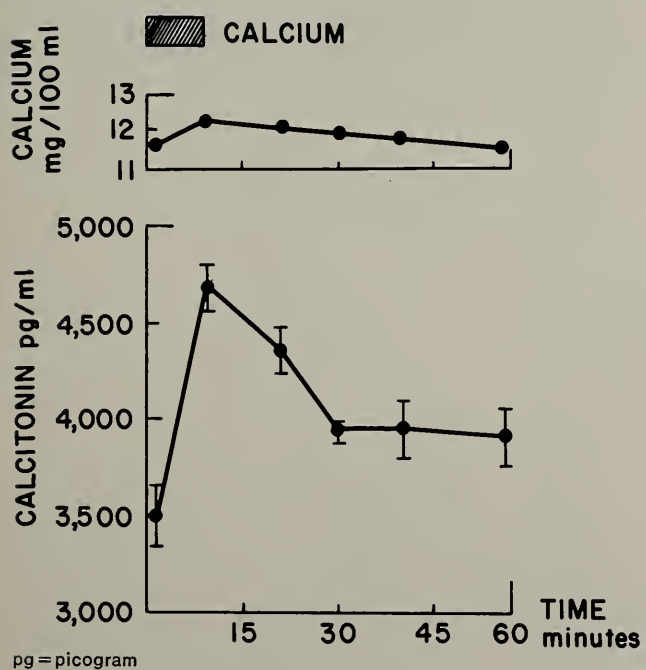


Figure 4.—Stimulatory effect of a short calcium (150 mg) infusion (shaded area) on plasma calcitonin in medullary thyroid carcinoma. The mean calcitonin and calcium changes for seven patients are shown. Bars represent standard errors (see Figures 3 and 5).

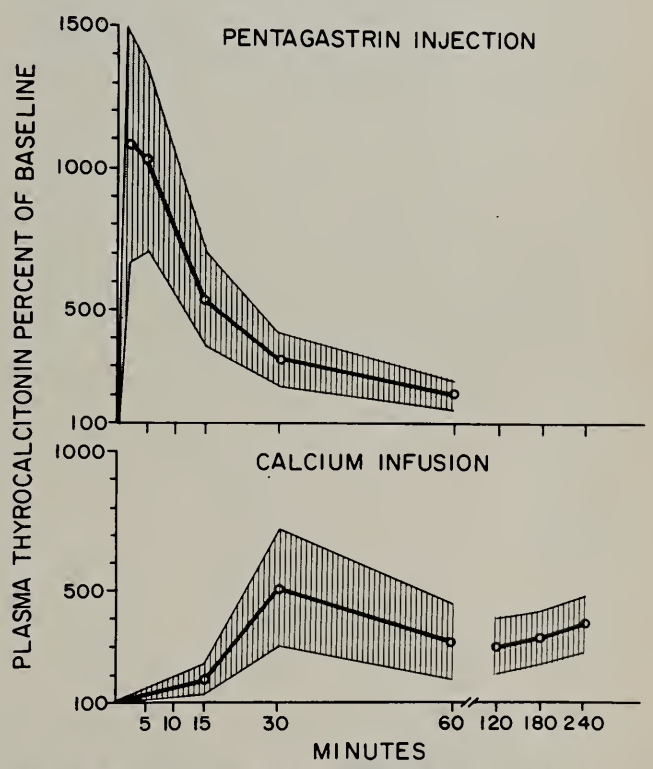
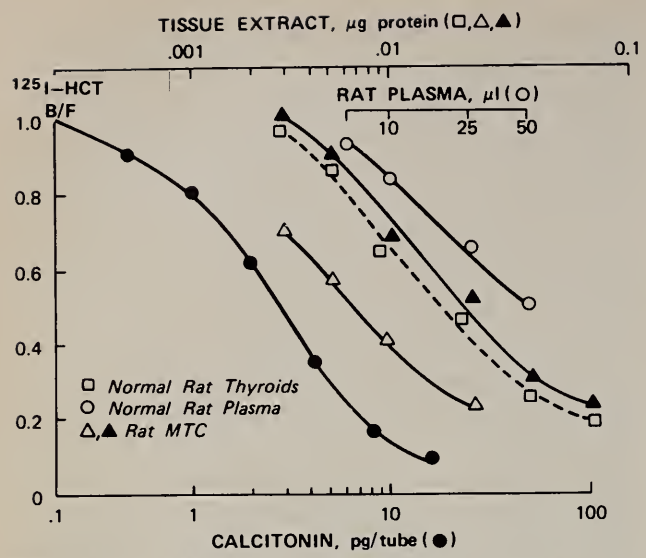


Figure 5.—Combined responses of seven patients with elevated baseline levels of plasma thyrocalcitonin (TCT) to pentagastrin injection and calcium infusion. Each patient received both tests on separate days wih pentagastrin injection being the initial test in four of the patients and calcium infusion being the initial test in three of the patients. Responses are expressed as the percent increase in immunoreactive TCT above initial baseline levels. Open circles and solid lines represent the mean responses and the shaded areas indicate the range of the standard errors. (Reproduced with permission from the authors and publisher from: Hennessy JF, Wells SA Jr, Ontjes DA, et al: A comparison of pentagastrin injection and calcium infusion as provocative agents for the detection of medullary carcinoma of the thyroid. J Clin Endocrinol Metab 39:487-495, 1974.)



^{125}I-HCT = human calcitonin MTC = medullary thyroid carcinoma
B/F = bound/free

Figure 6.—Measurement by radioimmunoassay of the calcitonin in peripheral rat plasma (during induced hypercalcemia), normal rat thyroid and rat medullary thyroid carcinoma (MTC). The two tumors represented are third and fourth transplantation generations, respectively (see references 60, 61).

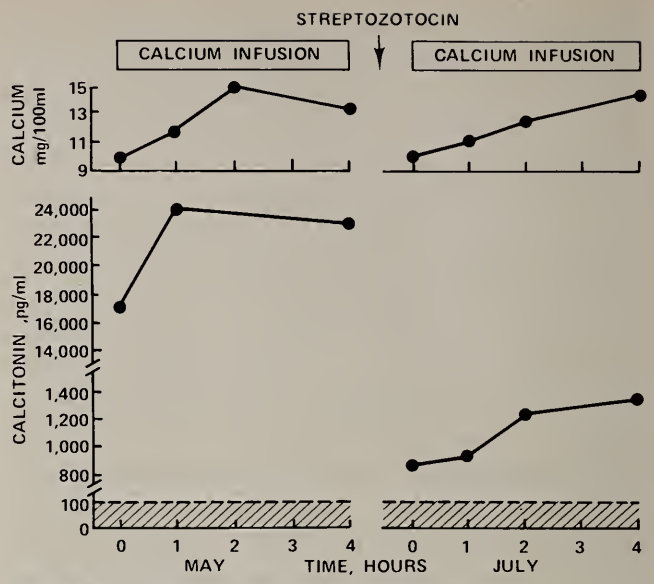


Figure 8.—Ectopic calcitonin production by an islet cell carcinoma of the pancreas. The tumor cells were shown to contain calcitonin by an immunoperoxidase procedure. Calcium infusion (15 mg per kg of body weight every three hours) stimulated calcitonin secretion by the tumor before and after streptozotocin therapy. There was a pronounced decrease in plasma calcitonin following streptozotocin therapy.

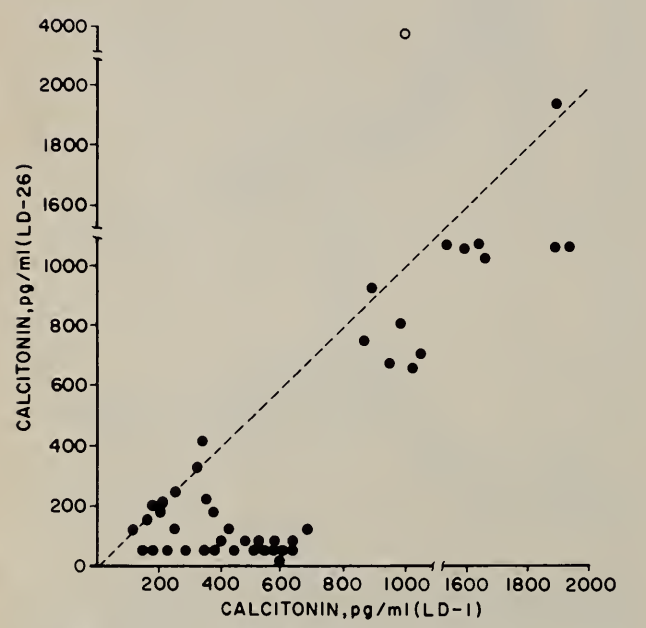
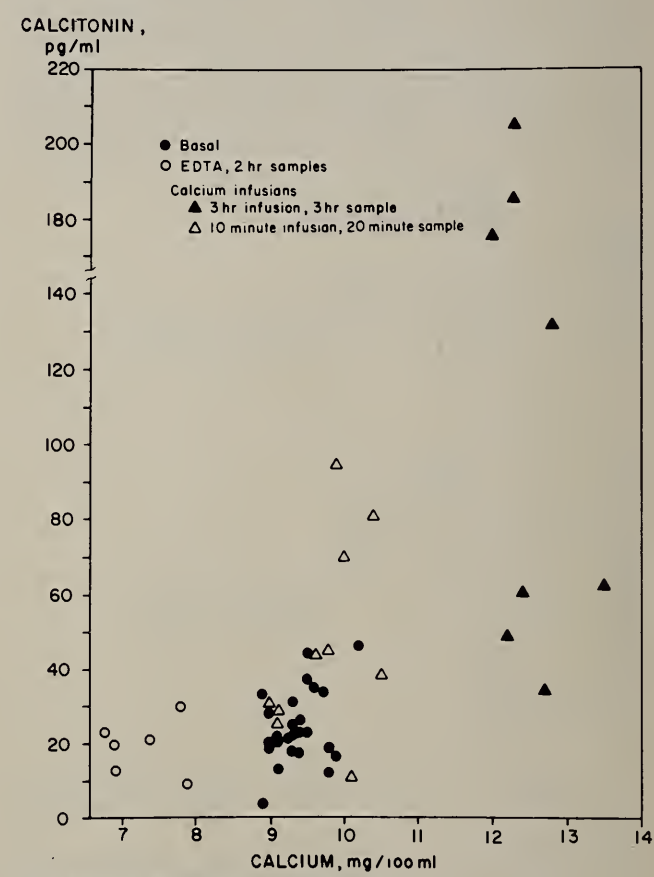


Figure 7.—Stimultaneous determination using two antisera (LD-1 and LD-26) of calcitonin in 44 plasma samples from 13 patients with medullary thyroid carcinoma (●), and one patient with a calcitonin-producing islet cell carcinoma of the pancreas (o). LD-1 gives a generally greater (or equal) estimate of calcitonin concentration in all of the samples than does LD-26 except for the patient with the pancreatic tumor and ectopic calcitonin production (o). Dashed line represents the relationship between the two calcitonin measurements which would exist if both of the antisera give indistinguishable results. (Assay limits 100 picograms per ml.)



EDTA = ethylene diamine tetracetic acid

Figure 9.—Immunoassayable calcitonin concentrations in normal subjects during the basal state (●) and during functional tests of hormone secretion (o, △, ▲).

TABLE 4.—*Principal Feature of Multiple Endocrine Adenomatosis*

TYPE II	
Medullary thyroid carcinoma	Hyperparathyroidism
Pheochromocytoma	Mucosal neuromata

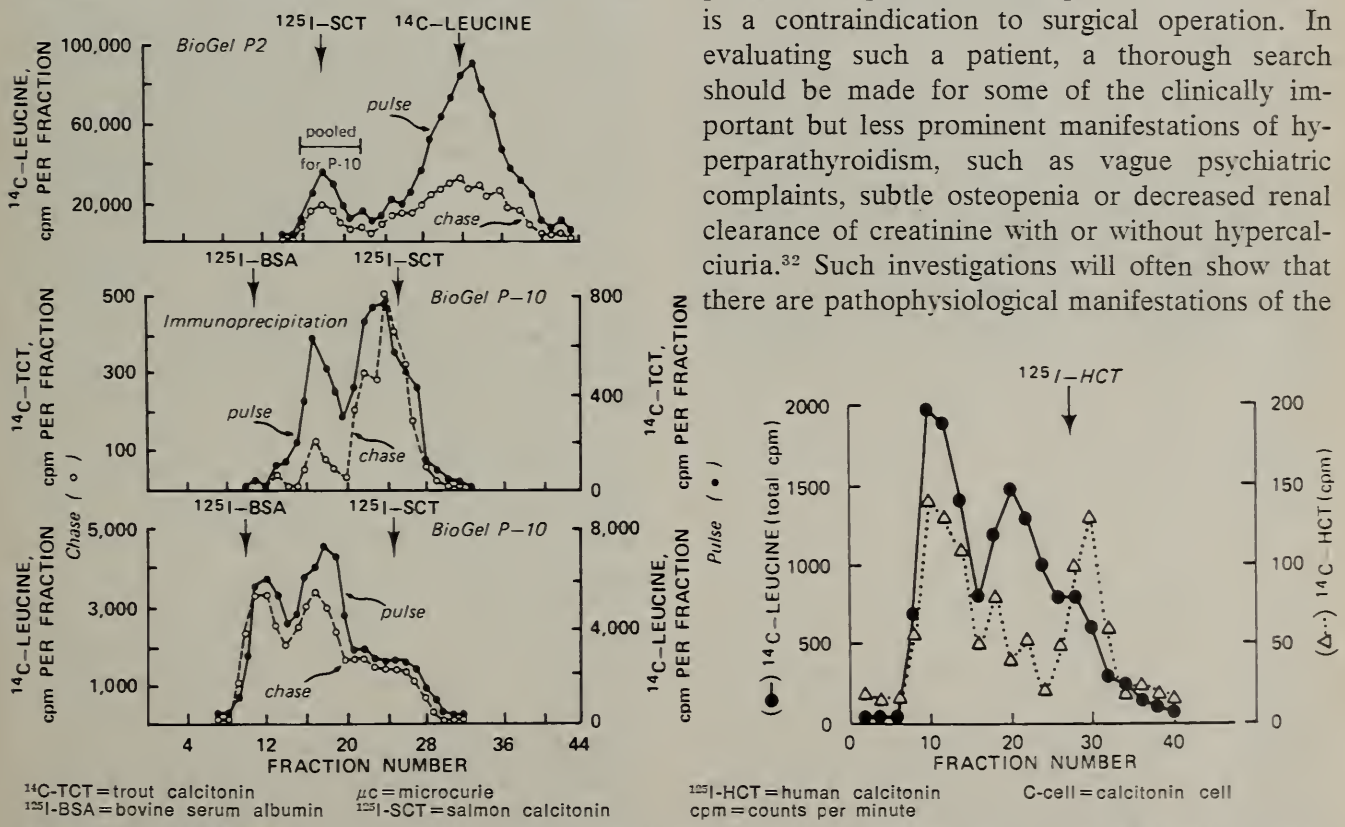
TABLE 5.—*Malignancies Associated with Calcitonin Production**

Medullary thyroid carcinoma	Carcinomas
Carcinoids	Maxillary antrum
Pheochromocytomas	Tongue
Melanoma	Pharynx
Pancreatic islet cell carcinoma	Parotid
Lymphoma	Tonsil
Seminoma	Prostate
Liposarcoma	Ovary
Astrocytoma	Rectum
Carcinoid Tumor	Uterus
Bronchial	Bladder
Intestinal	Stomach
Gastric	Cervix
Hodgkin's disease	Breast
	Lung

*Prepared from references 63-67 and authors' experience.

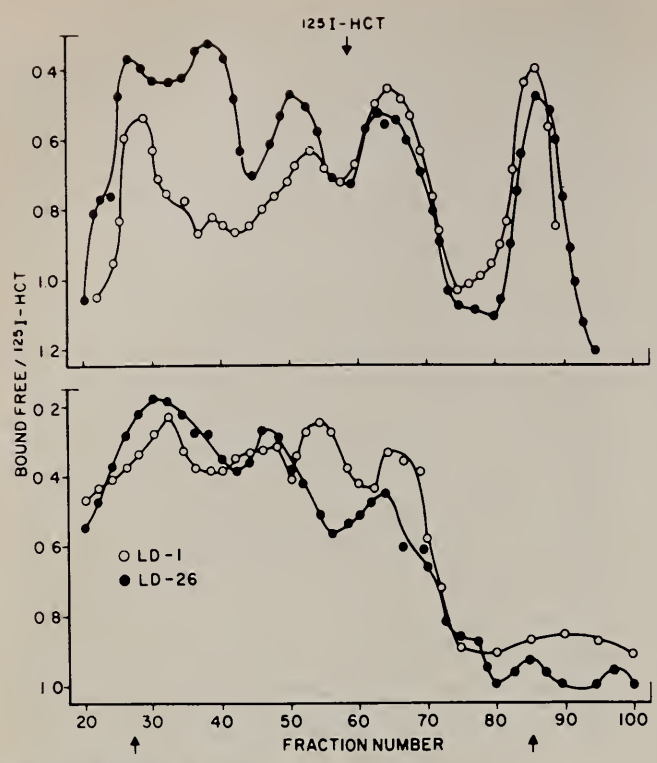
Asymptomatic Hyperparathyroidism

The clinical situation of asymptomatic hyperparathyroidism occurs when a patient is discovered to have a blood calcium level that is elevated, usually minimally, during a screening panel of blood chemistries. Further evaluation—such as x-ray studies (on industrial film) of the hands and clavicles (areas that are most sensitive radiographically to an excess of parathyroid hormone), blood PTH and phosphate determination, and lack of evidence for any other cause of the hypercalcemia—establishes the presence of hyperparathyroidism. But the diagnosis is made so early in the course of the illness that the patient is apparently asymptomatic. This situation presents a physician with a therapeutic dilemma—should he recommend surgical operation or follow the course of the patient? A prospective study is in progress to attempt to answer this question.[31] Until conclusive data are compiled, it is probably prudent to operate in most patients, unless there is a contraindication to surgical operation. In evaluating such a patient, a thorough search should be made for some of the clinically important but less prominent manifestations of hyperparathyroidism, such as vague psychiatric complaints, subtle osteopenia or decreased renal clearance of creatinine with or without hypercalciuria.[32] Such investigations will often show that there are pathophysiological manifestations of the



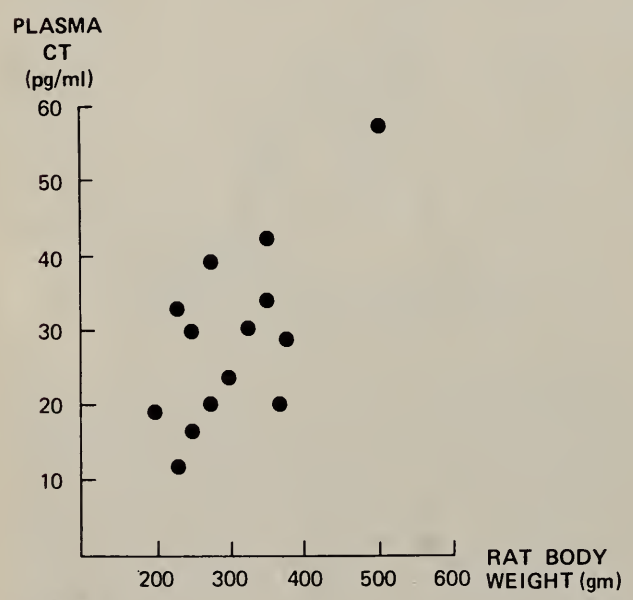
^{14}C-TCT = trout calcitonin
^{125}I-BSA = bovine serum albumin
μc = microcurie
^{125}I-SCT = salmon calcitonin
^{125}I-HCT = human calcitonin
cpm = counts per minute
C-cell = calcitonin cell

Figure 10.—Left Panel, Gel chromatography of acid soluble C-cell proteins obtained from pulse-chase experiments. After 14-hour preincubation, duplicate tubes of trout C-cell suspensions (10^6 cells/tube) were labelled with [^{14}C] leucine (7.5 μc/ml) for five hours. At this time 0.10 ml of 50 mM [^{12}C] leucine in Hank's salt solution was added to the "chase" tube, while the "pulse" tube received 0.10 ml of Hank's salt solution containing no leucine. Incubations were continued for an additional eight hours before homogenization and extraction of acid-soluble proteins. The pulse (•) and chase (o) samples were separately chromatographed on Bio Gel® P-2 and total [^{14}C] radioactivity of each column fraction was determined **(top panel).** The excluded volume from the P-2 column was then chromatographed on Bio-Gel P-10 and total [^{14}C] radioactivity (**bottom panel**) and immunoprecipitable, radiolabelled trout calcitonin ([^{14}C]TCT) **(middle panel)** was determined for each fraction. The **Right Panel** shows similar findings for monolayer tissue cultures of calcitonin-producing cells derived from medullary carcinomas of the thyroid.



125I-HCT = human calcitonin

Figure 11.—Gel (Bio Gel® P-30) filtration pattern of immunoreactivity in the plasma calcitonin from a patient with medullary thyroid carcinoma **(bottom)** and islet cell carcinoma of the pancreas **(top)** as measured by two anticalcitonin antisera, LD-1 and LD-26. The thyroidal **(bottom)** and nonthyroidal **(top)** calcitonin have different elution patterns. In addition, within each sample the two different antisera also yield different elution patterns of immunoreactivity. Arrows at bottom define void and salt volumes of column, respectively. Elution position of labelled calcitonin is also shown by arrow.



CT = calcitonin

Figure 12.—Immunoassayable calcitonin in the peripheral plasma of Wistar rats of varying weight (age).

hyperparathyroidism present and therefore provide a clear indication for surgical operation. But, the final judgment must be made by considering all of the clinical features in the patient.

Normocalcemic Hyperparathyroidism

Although similar in some respects, the case of a patient with normocalcemic hyperparathyroidism is likely to be the obverse in many ways to that of a patient with asymptomatic hyperparathyroidism. A common presentation is a patient who has repeated episodes of renal stones which are refractory to treatment. Most calcium determinations are within normal limits but the patient comes to surgery, the decision perhaps supported by an elevated plasma PTH, where abnormal parathyroid tissue may or may not be found.[33,34] While it is possible that some cases of normocalcemic hyperparathyroidism exist, it is equally likely that they are rare and that alternative explanations exist for the clinical course. In many of the cases of reported normocalcemic hyperparathyroidism, the patients had calcium levels that were continually near or at the upper limit of normal or even intermittently above the normal range.[33-35] The normal range of blood calcium is subject to age- and sex-related constraints which are not usually applied routinely by most clinical laboratories. The total blood calcium level is also subject to artifacts introduced by venous stasis during blood drawing and changes in blood protein concentrations.[1] Limited comparisons of total calcium measurements (usually by atomic absorption spectrophotometry) and ionic calcium measurements have shown the superiority of the ionic method for identifying abnormal values.[36] However, this procedure is not yet suitable for routine clinical application.[37]

All of these technical considerations would suggest that most patients who are diagnosed as having normocalcemic hyperparathyroidism actually have hyperparathyroidism with a minimally or intermittently elevated blood calcium level—or both. The identification of such patients is another result of the better appreciation of the manifestations of primary hyperparathyroidism and of its earlier diagnosis. Parenthetically, it is unlikely that normocalcemic hyperparathyroidism can produce hypercalciuria and nephrolithiasis. The hypercalciuria of hyperparathyroidism is due to the hypercalcemia which produces an increased filtered load of calcium. In fact, parathyroid hormone acts to *decrease* renal calcium clearance.

Therefore, in order to explain hypercalciuria in the face of a normal total calcium concentration and an elevated PTH, one would have to postulate that there is an increase in the filtered load of calcium without an increase in total blood calcium. Future studies of the importance of endogenous calcitonin secretion in nephrolithiasis may help to clarify the importance of this hormone in pathogenesis and it is of course possible that some of these patients have renal hypercalciuria and secondary hyperparathyroidism.[25,33]

Osteoporosis

Osteoporosis is a common disease that continues to be frustrating to physicians. No significant advances have been made in its treatment, and its pathogenesis remains obscure.[1] Some recent studies suggest that parathyroid gland dysfunction may play a role in a small percentage of patients with osteoporosis but the data are conflicting.[38,39] However, parathyroid hormone determination may be of some clinical value in osteoporotic patients. An increase in hormone concentration may offer a clue to the presence of complicating osteomalacia. If the presence of osteomalacia can be confirmed, the osteomalacic component of the osteopenic state could then be treated with vitamin D.

Calcitonin

Calcitonin can be considered to be in many ways the physiological antagonist of parathyroid hormone.[1] The biochemistry and biology of this hormone and its usefulness in the treatment of some hypercalcemic states are thoroughly considered in several reviews.[1,4,5,40,43] This discussion will focus on the importance of calcitonin in the treatment of Paget's disease and in the diagnosis of medullary thyroid carcinoma and other neoplastic disorders.

Paget's Disease

Significant progress has been made in the management of patients with Paget's disease.[1,42] Several forms of therapy are now available for effective treatment of the illness.[1] The regimen that seems to offer the greatest therapeutic effect in combination with the fewest untoward effects is the use of calcitonin. Clinical trials with calcitonin are now over and the salmon form of the drug is commercially available as Calcimar®. Calcitonin acts to reverse the primary pathological defect in Paget's disease—increased bone resorption. Treatment with calcitonin reverses the increased plasma alkaline phosphatase and the increased urinary hydroxyproline and has been reported to produce histological and x-ray changes in bone toward normal.[44] Not all patients with Paget's disease who are treated with calcitonin respond to the drug. Furthermore, some patients respond only partially and some patients become refractory to its effects after several months of therapy. The development of antibodies to salmon calcitonin may account for some treatment failures.[1,42] The availability of human calcitonin may be useful in some patients. It has also been suggested that chronic calcitonin administration may result in secondary hyperparathyroidism.[45] However, contrary reports have also appeared and the resolution of this controversy awaits further study.[46] Calcitonin is relatively safe with its major side effect being nausea. A disadvantage of the drug is that it has to be taken parenterally. But, most patients receive sufficient symptomatic benefits from its administration that they readily learn to administer calcitonin to themselves.

Medullary Thyroid Carcinoma

It has become well-established during the past several years that plasma calcitonin measurement by radioimmunoassay offers an accurate and reliable test for the diagnosis of medullary thyroid carcinoma.[47-53] This tumor is a malignancy of the calcitonin-producing cells of the thyroid gland.[1] It can occur sporadically or in a familial pattern which is transmitted with an autosomal dominant inheritance pattern.[54] As a familial tumor it is part of one of the multiple endocrine adenomatoses, MEA Type II (Table 4).

The incidence of medullary thyroid carcinoma has not been carefully established since its existence as a distinct pathological entity has only been appreciated for one decade. Although the tumor is now being diagnosed with increased frequency, it is not likely to be a common tumor in a general epidemiological sense. However, its general epidemiological importance is far outweighed by the dominant inheritance pattern of the familial form of the tumor. Once the diagnosis is made in a given patient, a careful family search is likely to turn up affected relatives. This becomes a therapeutically important consideration since the application of the calcitonin assay can establish the presence of the tumor very early in its course[1,55,56]—so early that there may be no

clinical manifestations of the tumor and it may be confined to the thyroid and, therefore, curable by thyroidectomy. This can often be done by the relatively simple measurement of calcitonin by radioimmunoassay in a peripheral plasma sample of the patient. In most patients with medullary thyroid carcinoma, the basal level of the hormone will be diagnostically elevated. However, a significant percentage of patients may have basal levels of calcitonin which are indistinguishable from normal (Figure 2). In these patients, provocative tests of calcitonin secretion may be used to establish the diagnosis. Three procedures are currently being used for provocative testing: long (two to four hour) calcium infusion, gastrin infusion and short (ten minute) calcium infusion.[48,50,56,57] The long calcium infusion has been most extensively used and experience with it has established its reliability (Figure 3). The shortened (10 minute) calcium infusion also seems reliable but experience with it is less extensive (Figure 4). The short infusion is more convenient and less likely to cause any untoward consequences of induced hypercalcemia.

Gastrin also appears to be a reliable provocative test for calcitonin secretion (Figure 5). Its disadvantages are that its administration produces chest discomfort and that it is still considered an experimental agent for this indication and, therefore, is not as readily available. The immunoassay can also be used in conjunction with selective venous catheterization for diagnostic purposes.[58] This procedure can help to define the extent and location of the malignancy and can perhaps lead to even earlier diagnosis than is offered by provocative testing.

The recent development of an immunoassay for rat calcitonin[59-61] and the identification of a rat form of medullary thyroid carcinoma[60-62] will provide an experimental model for the systematic study of this tumor (Figure 6).

Ectopic Calcitonin Production

As important as the calcitonin immunoassay has become in the early and reliable diagnosis of medullary thyroid carcinoma, recent observations indicate that the clinical value of this procedure may become even more important. It has been observed during the last several years that tumors other than medullary thyroid carcinoma may be associated with excess calcitonin production.[63-67] It was first considered that this represented a common embryological origin for the calcitonin-producing cells, since these tumors—like medullary thyroid carcinoma—were usually of neural crest origin.[63] However, the large variety of tumors that have been now reported in association with elevated plasma calcitonin are not consistent with this explanation (Table 5). In fact, there is some evidence to suggest that the nonthyroidal calcitonin produced by some tumors is immunochemically distinct from thyroidal (medullary thyroid carcinoma) calcitonin (Figure 7).

Not all tumors associated with hypercalcitoninism have been shown to produce excess calcitonin; in fact this has only been directly shown for a few (Figure 8). Therefore, other explanations may exist for this hypercalcitoninism of malignancy. The tumor may be secreting a calcitonin secretagogue or it may have metastasized to bone where it is stimulating the secretion of thyroidal calcitonin by (1) destroying bone and producing an autoinfusion of calcium or (2) causing the release of an endogenous bone factor which stimulates the secretion of calcitonin in order to counteract the increased resorption produced by the metastases. Whichever of these explanations pertains, an increased plasma calcitonin can be the signal for a variety of metastatic disorders. It is to be hoped that hypercalcitoninism will be as early a signal for these other tumors as it has been for medullary thyroid carcinoma.

Calcitonin in Physiology and Pathophysiology

In contrast to the events that attend the discovery of many new hormones, the discovery of calcitonin was followed by an appreciation of its importance in pathology (medullary thyroid carcinoma) and pharmacology (treatment of Paget's disease and hypercalcemia) rather than its role in normal physiology. In fact, the role of calcitonin in normal physiology has not been well-defined. Progress in such studies was limited by the difficulties of measuring the low concentrations of this potent hormone which circulate in human plasma. However, improved assay techniques are now available for these experiments. Preliminary clinical studies indicate that circulating levels of calcitonin are responsive to pertubations of calcium and bone mineral homeostasis (Figure 9) and gastrointestinal physiology and that secondary as well as primary disorders of calcitonin secretion exist.[17,68-73] These studies indicate that the biosynthesis, secretion and metabolism of calcitonin may be as complicated as for

parathyroid hormone. A biosynthetic precursor (procalcitonin) for calcitonin has been identified (Figure 10) and multiple immunoreactive forms of the hormone have been shown in both human (Figure 11) and rat[60,74,75] plasma. There is even some evidence that calcitonin may have a biological role not directly related to bone mineral metabolism. And, the development of an immunoassay for rat calcitonin has already produced some unanticipated findings in this animal model for calcitonin physiology (Figure 12). These preliminary observations will serve as a framework for clinical and experimental studies conducted in the next several years to identify the physiological and pathophysiological significance of calcitonin.

REFERENCES

1. Potts JT, Deftos LJ: Parathyroid hormone, calcitonin, Vitamin D, bone and bone mineral metabolism, *In* Duncan's Diseases of Metabolism, 7th Ed. Philadelphia, W. B. Saunders Co., 1974, p 1225

2. Reiss E, Canterbury JM: Emerging concepts of the nature of circulating parathyroid hormones: Implications for clinical research. Recent Prog Horm Res 30:391-429, 1974

3. Arnaud CD: Radioassay of the calcitrophic hormones. Metabolism 22:1013-1020, 1973

4. Munson PL, Cooper CW, Gray TK, et al: Physiological significance of calcitonin, *In* Taylor S (Ed): Endocrinology 1973. William Heinemann Medical Books, 1974, p 131-142

5. Queener SF, Bell NH: Calcitonin: A general survey. Metabolism 24:555-567, 1974

6. Schneider AB, Sherwood LM: Calcium homeostasis and the pathogenesis and management of hypercalcemic disorders. Metabolism 23:975-1007, 1974

7. DeLuca HF: Vitamin D today. DM:March 1975

8. Avioli LV, Haddad JG: Vitamin D: Current concepts. Metabolism 22:507-531, 1973

9. Coburn JW, Hartenbower DL, Norman AW: Metabolism and action of the hormone Vitamin D. West J Med 121:22-44, 1974

10. Hamilton JW, MacGregor RR, Chu LLH, et al: The isolation and partial purification of a non-parathyroid hormone calcemic fraction from bovine parathyroid glands. Endocrinology 89:1440-1447, 1971

11. Habener JF, Kemper B, Potts JT Jr, et al: Proparathyroid hormone: Biosynthesis by human parathyroid adenomas. Science 178:630-633, 1972

12. Wong ET, Lindall AW: Preliminary evidence for a microsomal precursor to human parathyroid hormone. Proc Natl Acad Sci USA 70:2291-2294, 1973

13. Kemper B, Habener JF, Mulligan RC, et al: Pre-proparathyroid hormone—A direct translation product of parathyroid messenger RNA. Proc Natl Acad Sci USA 71:3731-3735, 1974

14. Cohn DV, MacGregor RR, Luke LH, et al: Biosynthesis of proparathyroid hormone and parathyroid hormone. Am J Med 56:767-773, 1974

15. Segre GV, Habener JF, Powell D, et al: Parathyroid hormone in human plasma. J Clin Invest 51:3163-3172, 1972

16. Silverman R, Yalow RS: Heterogeneity of parathyroid hormone. J Clin Invest 52:1958-1971, 1973

17. Deftos LJ, Parthemore JG: Secretion of parathyroid hormone in patients with medullary thyroid carcinoma. J Clin Invest 54:416-420, 1974

18. Williams GA, Peterson WC, Bowser EN, et al: Interrelationship of parathyroid and adrenocortical function in calcium homeostasis in the rat. Endocrinology 95:707-712, 1974

19. Deftos LJ, Miller E, Parthemore JG, et al: Changes in parathyroid hormone (PTH) secretion unrelated to changes in blood calcium. Clin Res 23:110A, 1975

20. Deftos LJ, Parthemore JG, Miller E, et al: PTH secretion —Regulation by non-ionic factors. Clin Res 23:317A, 1975

21. Riggs BL, Arnaud CD, Reynolds JC, et al: Immunologic differentiation of primary hyperparathyroidism from hyperparathyroidism due to nonparathyroid cancer. J Clin Invest 50:2079-2083, 1971

22. Powell D, Singer FR, Murray TM, et al: Nonparathyroid humoral hypercalcemia in patients with neoplastic diseases. N Engl J Med 289:176-181, 1973

23. Tashjian AG Jr, Voelkel EF, Levine L, et al: Evidence that the bone resorption-stimulating factor produced by mouse fibrosarcoma cells is prostaglandin E_2. J Exp Med 136:1329-1343, 1972

24. Mundy GR, Raisz LG, Cooper RA, et al: Evidence for the secretion of an osteoclast stimulating factor in myeloma. N Engl J Med 291:1041-1046, 1974

25. Coe FL, Canterbury JM, Firpo JJ, et al: Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. J Clin Invest 52:134-142, 1973

26. Smith LH, Thomas WC Jr, Arnaud CD: Ortho-phosphate therapy in calcium renal lithiasis, *In* Proceedings of the Symposium on Renal Stone Research, Madrid, Spain (In press)

27. Pak CYC, Ohata M, Lawrence EC, et al: The hypercalciurias: Causes, parathyroid function, and diagnostic criteria. J Clin Invest 54:387-400, 1974

28. Nordin BEC, Peacock M, Wilkinson R: Hypercalciuria and calcium stone disease, *In* MacIntyre I (Ed): Clinics in Endocrinology and Metabolism, Vol 1, Philadelphia, W. B. Saunders Co., 1972, pp 169-183

29. Reiss E. Canterbury JM: Spectrum of hyperparathyroidism. Am J Med 56:794-799, 1974

30. Deftos LJ: Parathyroid hormone, *In* Jaffe BM, Behrman HR (Eds): Methods of Hormone Radicimmunoassay. New York, Academic Press, Inc. 14:231-247, 1974

31. Purnell DC, Scholz DA, Smith LH, et al: Treatment of primary hyperparathyroidism. Am J Med 56:800-809, 1974

32. Arnaud CD: Introduction to the Third Keating Memorial Symposium. Am J Med 56:743-750, 1974

33. Reiss E: Hyperparathyroidism—Current prospectives. Adv Intern Med 19:287, 1974

34. Sheiber W, Birge SJ, Avioli LV, et al: Normocalcemic hyperparathyroidism with normal parathyroid glands. Arch Surg 103:299-302, 1971

35. Johnson RD, Conn JW: Hyperparathyroidism with a prolonged period of normocalcemia. JAMA 210:2063-2066, 1969

36. Low JC, Schaaf M, Earll JM, et al: Ionic calcium determination in primary hyperparathyroidism. JAMA 223:152-155, 1973

37. Loken HF, Eastman JW: Calcium measurements in hyperparathyroidism. JAMA 223:188-189, 1973

38. Riggs BL, Arnaud CD, Jowsey J, et al: Parathyroid function in primary osteoporosis. J Clin Invest 52:181-184, 1973

39. Berlyne GM, Ben-Ari J, Galinsky D, et al: The etiology of osteoporosis. JAMA 229:1904-1905, 1974

40. Copp DH: Endocrine regulation of calcium metabolism. Annu Rev Physiol 32:61-86, 1970

41. Habener JF, Niall H: Hormonal regulation of calcium metabolism, *In* Rickenberg HV (Ed): Biochemistry of Hormones. University Park Press, 1974, pp 101-152

42. Singer FR: Treatment of Paget's disease of bone. Postgrad Med 57:117-120, Mar 1975

43. Avramides A, Baker RK, Wallach S: Metabolic effects of synthetic salmon calcitonin in Paget's disease of bone. Metabolism 23:1037-1046, 1974

44. Woodhouse NJY, MacIntyre I, Joplin GF, et al: Radiological regression in Paget's disease treated by human calcitonin. Lancet 2:992-994, 1972

45. Dube WJ, Goldsmith RS, Arnaud SB, et al: Hyperparathyroidism secondary to long term therapy of Paget's disease of bone with calcitonin. Excerpta Medica International Congress Series No 243, pp 113-115, 1971

46. Bruckhardt PM, Singer FR, Potts JT Jr: Parathyroid function in patients with Paget's disease treated with salmon calcitonin. Clin Endocrinol (Oxf) 2:15-22, 1973

47. Clark MB, Boyd GW, Byfield PGH: A radioimmunoassay for human calcitonin M. Lancet 2:74, 1969

48. Tashjian AH Jr, Howland BG, Melvin KEW, et al: Immunoassay of human calcitonin. N Engl J Med 283:890-895, 1970

49. Deftos LJ: Immunoassay for human calcitonin. Metabolism 20:1122-1128, 1971

50. Hennessy JF, Wells SA, Ontjes DA, et al: A comparison of pentagastrin injection and calcium infusion as provocative agents for the detection of medullary carcinoma of the thyroid. J Clin Endocrinol Metab 39:487-495, 1974

51. Sizemore GW, Go VLW, Kaplan EL, Sanzenbacher LJ, et al: Relations of calcitonin and gastrin in the Zollinger-Ellison syndrome and medullary carcinoma of the thyroid. N Engl J Med 288:641-644, 1973

52. Silva OL, Snider RH, Becker KL: Radioimmunoassay of calcitonin in human plasma. Clin Chem 20:337-339, 1974

53. Samaan NA, Hill CS Jr, Beceiro JR, et al: Immunoreactive calcitonin in medullary carcinoma of the thyroid and in maternal and cord serum. J Lab Clin Med 81:671-681, 1973

54. Steiner AL, Goodman AD, Powers SR: Multiple endocrine neoplasia, Type 2. Medicine (Baltimore) 47:371-409, 1968

55. Melvin KEW, Miller HH, Tashjian AR Jr: Early diagnosis of medullary carcinoma of the thyroid gland by means of calcitonin assay. N Engl J Med 285:1115-1120, 1971

56. Deftos LJ: Radioimmunoassay for calcitonin in medullary thyroid carcinoma. JAMA 227:403-406, 1974

57. Parthemore JG, Deftos LJ: A short calcium (Ca) infusion in the diagnosis of medullary thryroid carcinoma (MTC). Clin Res 22:494A, 1974

58. Goltzman D, Potts JT Jr, Ridgeway EC, et al: Calcitonin as a tumor marker. N Engl J Med 290:1035-1039, 1974

59. Burford HJ, Ontjes DA, Cooper CW, et al: Purification, characterization and radioimmunoassay of thyrocalcitonin from rat thyroid glands. Endocrinology 96:340-348, 1975.

60. Roos BA, Deftos LJ: Radioimmunoassay of peripheral plasma and thyroidal rat calcitonin. J Lab Clin Med (In press)

61. Deftos LJ, Boorman GA, Roos BA: Immunoassay of calcitonin in rat medullary thyroid carcinoma. Horm Metab Res (In press)

62. Boorman GA, Heersche JNM, Hollander CF: Transplantable calcitonin-secreting medullary carcinomas of the thyroid in the WIG/rij rat. J Natl Cancer Inst 53:1011-1015, 1974

63. Milhaud G, Calmette C, Jullienne A, et al: A new chapter in human pathology: Calcitonin disorders and therapeutic use, *In* Talmage RV, Munson PL (Eds): Calcium, Parathyroid Hormone, and the Calcitonins. Excerpta Medica, 1972, pp 56-70

64. Silva OL, Becker KL, Primack A, et al: Ectopic secretion of calcitonin by oat-cell carcinoma. N Engl J Med 290:1122-1123, 1974

65. Milhaud G, Calmette C, Taboulet J, et al: Hypersecretion of calcitonin in neoplastic conditions (Letter). Lancet 1:462, 1974

66. Coombes RC, Hillyard C, Greenberg PB, et al: Plasma-immunoreactive-calcitonin in patients with non-thyroid tumors. Lancet 1:1080-1083, 1974

67. Deftos LJ, Rosen SW, Sartiano GP: Simultaneous ectopic production of parathyroid hormone (PTH) and calcitonin (CT). Clin Res 22:486A, 1974

68. Deftos LJ, Powell D, Parthemore JG, et al: Secretion of calcitonin in hypocalcemic states in man. J Clin Invest 52:3109-3114, 1973

69. Samaan NA, Anderson GD, Adam-Mayne ME: Immunoreactive calcitonin in the mother, neonate, child, and adult. Am J Obstet Gynecol 121:622-625, 1975

70. Silva OL, Becker KL, Selawry HP, et al: Human calcitonin and serum phosphate. Lancet 1:1055, 1974

71. Heynen G, Franchimont P: Human calcitonin radioimmunoassay in normal and pathological conditions. Eur J Clin Invest 4:213-222, 1974

72. Deftos LJ, Parthemore JG: Measurement of calcitonin (CT) in normal human plasma by immunoextraction (IEX) and radioimmunoassay (RIA). Clin Res 22:465A, 1974

73. Parthemore JG, Deftos LJ: The regulation of calcitonin in normal human plasma as assessed by immunoprecipitation and immunoextraction. J Clin Invest 56:835-841, 1975

74. Singer FR, Habener JF: Multiple immunochemical forms of calcitonin in plasma. Biophys Biochem Res Comm 61:660, 1974

75. Deftos LJ, Roos BA, Bronzert D, et al: Immunochemical heterogeneity of calcitonin in plasma. J Clin Endo Metab 40: 409-412, 1975

Prophylactic Antibiotics

One part of prophylactic antibiotics that is the biggest myth that has ever been perpetrated is the value of antimicrobial bowel prep. Every chapter that is written in standard American textbooks about surgical operation on the colon starts out with an erroneous, but well-intentioned, statement that all of the good things come as a result of the frequent use of antimicrobial bowel preparation with sulfa and neomycin and whatnot. You will remember that Edgar Poth's initial experiments with these drugs showed benefit only in a situation in which the blood supply to the bowel was impaired. Now, if you want to do your colon anastomosis with faulty blood supply, you can, but I think I can beat you any day of the week by using good blood supply. There is no place for intraluminal antimicrobial agents in surgical operation on the large intestine unless one is going to deal with impaired blood supply. Now, there is one clinical setting where we regularly do this and that is with patients who have aortic aneurysms resected in which we suspect or think that the inferior mesenteric artery is patent. That is an induced form of intestinal ischemia. And there are good data, largely from the Mayo Clinic, that show about a 4 percent incidence of clinical ischemic colitis if you do not use a bowel preparation, and that this largely disappears if you do. But for a person in whom colon resection is being done, bowel prep contributes nothing.

—HIRAM C. POLK, JR., MD, *Louisville*

Extracted from *Audio-Digest Surgery*, Vol. 22, No. 2 in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057

Specialty Conference

Refer to: Mendoza SA, Mendoza G: Hemolytic-uremic syndrome —Pediatric Grand Rounds, University of California, San Diego, and University Hospital, San Diego (Specialty Conference). West J Med 123:459-466, Dec 1975

Participants

STANLEY A. MENDOZA, MD
GUILLERMO MENDOZA, MD

Taken from the weekly Pediatric Grand Rounds held at the University Hospital, University of California, San Diego, Medical Center, San Diego.

Hemolytic-Uremic Syndrome

GUILLERMO MENDOZA:* The patient for discussion this morning is a 6-year-old white boy who presented with a history of six days of mild gastroenteritis that progressed to vomiting with abdominal pain and finally bloody diarrhea. Three days before admission to University Hospital, the patient was admitted to Mercy Hospital with this pattern of evolving symptoms. One day before admission here gross hematuria developed and appropriate studies were done again at that time to establish a diagnosis. A smear taken that evening showed definite microangiopathic changes which were not present on admission. Because of the presumed diagnosis of hemolytic-uremic syndrome the child was transferred to this hospital for dialysis. During the three days at Mercy Hospital, hematocrit fell from 42 to 23 percent. Platelets were originally adequate on smear, but dropped to 42,000 per cu mm. Blood urea nitrogen (BUN) climbed from 15 to 55 mg per 100 ml over the three days. The creatinine jumped from normal to 5.3 mg per 100 ml. The serum sodium concentration fell from 138 to 128 mEq per liter before hydration was adjusted. Leukocyte count when admitted to University Hospital was 19,000 per cu mm with 40 percent segmented cells and 40 percent band cells and a reticulocyte count of 4.2 percent.

On physical examination the heart rate was 136 and the respiratory rate was 24 with minimal distress. The patient was found to be pale, weak and mildly irritable. A Grade III/VI systolic murmur was heard at the left sternal border without radiation. The liver was 2 cm and spleen tip palpable. Neurologically, deep tendon reflexes were brisk symmetrically. The patient was light-headed and too weak to walk. By the time of transfer, he had been anuric for almost two days. We delayed peritoneal dialysis until the BUN reached 140 mg per 100 ml with a creatinine concentration of 8.6 mg per 100 ml. At that point the patient was moderately irritable, though his condition was otherwise unchanged from admission. Transfusion was carried out to a hematocrit of 28 percent. Dialysis was done initially for three days. The major difficulties during this time were hemolysis and thrombocytopenia without bleeding.

Having been anuric for 10 days, the patient began urinating on the eighth day in hospital. At that time, platelet count went from 14,000 to 48,000 per cu mm within one day. From this point on, the platelets made a very steady rise and renal function improved steadily. The patient was discharged two weeks after admission on a 20 gram protein diet. On follow-up five weeks later, BUN was 18 mg per 100 ml with a serum creatinine concentration of 0.7 mg per 100 ml. In summary, we have a six-year-old boy with hemolytic-uremic syndrome who was anuric for ten days and who appears to have achieved complete recovery.

STANLEY A. MENDOZA:† The case presented this morning is in some ways a typical case of the hemolytic-uremic syndrome (HUS). Before going further, however, it is necessary to modify that remark because the hemolytic-uremic syndrome does not seem to be a single entity. There is a clear difference in the hemolytic-uremic syndrome

*Resident in Pediatrics.

Reprint requests to: Stanley A. Mendoza, MD, Chief, Division of Pediatric Nephrology, Department of Pediatrics, University of California, San Diego, School of Medicine, La Jolla, CA 92093.

†Associate Professor of Pediatrics.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
GFR = glomerular filtration rate
HUS = hemolytic-uremic syndrome

as seen in different parts of the world. Very little is understood about the pathogenesis of the hemolytic-uremic syndrome. In the absence of such basic information, it is probably premature to talk about a typical case of the hemolytic-uremic syndrome. Nevertheless, this case is typical of the hemolytic-uremic syndrome as it is seen in California. The disease occurs here frequently and has been reported in detail by Tune, Lieberman, Piel and their co-workers.[1-4]

The major locale mentioned in discussions of HUS is Argentina. HUS appears to be about ten times as common in Buenos Aires as in other places in the world. In general, nephrologists will see 2 or 3 cases of HUS a year in the United States, while in Argentina there are 30 or more cases annually.[5-7] One significant difference between HUS in Argentina and in California is the age at which the disease occurs. In the series from Buenos Aires, the oldest child with HUS was 37 months of age and the mean age was 13 months. In Argentina, therefore, HUS is a disease of infancy. In the series from Stanford, the mean age was 4½ years. There were only two patients at Stanford who were as young as the mean age of the patients from Argentina and, conversely, in the series from Argentina the oldest child was younger than the mean age of the patients from Stanford. In California, therefore, HUS is a disease of young children, but usually not of infants. The patients we have seen in San Diego have been mostly in the age range of four to eight years.

Patients with hemolytic-uremic syndrome usually have a prodromal illness. Virtually all of the patients in California with the syndrome present with gastrointestinal symptoms. In Argentina or in Europe, about 50 percent of the patients present with upper respiratory symptoms. The prodromal gastrointestinal symptoms are more severe in California than in other parts of the world. It is common for the children to be admitted to hospital because of the severity of diarrhea. The patient presented this morning was, for example, admitted to hospital because of diarrhea. In the Stanford series of 28 patients, laparotomy was carried out in two during prodromal illness. In addition, there are several reports of patients diagnosed as having ulcerative colitis during the prodromal illness.[8,9] We have seen this recently as well. The prodrome is not only more severe in California, but also tends to be longer than in Argentina. In Argentina, the acute renal failure was coincident with the onset of the prodromal illness in over 50 percent of the cases. In the Stanford series, the prodrome started an average of seven days before the hemolytic and uremic components of the disease.

Because most of these children present with a prodromal illness which appears infectious in nature, there has been an intensive search for a causative organism. In addition to the fact that the children have a relatively uniform gastrointestinal prodrome, other things suggest an infectious cause for HUS. The disease is endemic in California. However, there have been several clearly defined epidemics as well. The most striking of these was in Wales, where the syndrome developed in ten patients within a few months in a small geographic area.[10] A variety of organisms have been isolated from patients with HUS. In particular, it is worth mentioning the isolation of a microtatobiote by Mettler[11] from two patients with HUS and one patient with thrombotic thrombocytopenic purpura. A microtatobiote is an organism similar to a rickettsia. Although this report caused considerable interest at the time, there have been no subsequent reports of the isolation of this organism in children with HUS. Viruses such as Coxsackie, ECHO 29 and arbovirus have been isolated from children with HUS. The arbovirus was isolated in Argentina. There is a disease called Argentinian hemorrhagic fever which is associated with this virus. A sizable number of patients with HUS in Buenos Aires have either had the virus or a rising antibody titer to it.[6] As far as I know, this virus has not been isolated in the United States.

Further evidence that HUS results from an environmental causative factor was obtained in a prospective collaborative study done at Stanford and the University of California, San Diego. In this study the siblings of 13 patients with HUS were tested for signs of the syndrome. Three siblings were observed with subclinical manifestations of HUS.[12]

The presenting complaints of patients with this illness are varied. As I mentioned, the prodromal symptoms are frequently so severe that the patient is admitted because of abdominal pain, diarrhea and weight loss. Other presenting complaints

are neurological symptoms such as seizures or coma, or symptoms of fluid overload, such as edema, hypertension or congestive heart failure. Occasionally there is a history of infrequent urination, but this is an unusual presenting complaint. On the other hand, pallor is a relatively common presenting complaint. I have seen a number of children with HUS who have had several days of vomiting or diarrhea. Then one morning the parents come into the child's room and find him spectacularly pale. These children are taken to a physician and hemoglobin concentrations are found to be in the range of 4 to 5 grams per 100 ml.

Manifestations of Hemolytic-Uremic Syndrome

What are the manifestations of the hemolytic-uremic syndrome? First, as we have already mentioned, there is a prodromal illness which is usually gastrointestinal. Second, there is a hemolytic anemia with microangiopathic changes of the red blood cells. Occasionally, there is evidence of hemolysis without actual anemia. In other words, in some patients there will be hemoglobin concentrations in the range of 10 to 12 grams per 100 ml with a high reticulocyte count and red blood cells with microangiopathic changes. The peripheral smear contains helmet cells, burr cells and a sizable proportion of abnormal fragmented-appearing red blood cells. The smear is so characteristic that it should be examined in any child with acute renal failure. In this way, it is possible to make a presumptive diagnosis of hemolytic-uremic syndrome very rapidly. This is the manner in which the diagnosis was confirmed in the child presented this morning. If findings on the smear are normal, the diagnosis of hemolytic-uremic syndrome becomes less likely. We have seen several children, however, in whom findings on first smears were essentially normal but in whom a typical microangiopathic smear was seen one or two days later. Most of the children with HUS are also thrombocytopenic but this is not invariable.

About two thirds of patients with HUS have oliguria. There seems to be some correlation between the severity of the oliguria and the eventual outcome for the patient. However, I cared for a child in Chicago who was not oliguric until four weeks into the illness when severe central nervous system symptoms developed and he died.

Patients with HUS have hematuria and proteinuria. The BUN is often quite high and tends to rise very rapidly because in these patients large numbers of red blood cells are breaking down and therefore more protein is being metabolized and more urea is being produced than in a normal patient. In an anephric patient on dialysis there usually is a BUN rise of about 20 mg per 100 ml per day. The increase in BUN in patients with hemolytic-uremic syndrome is often as great as 50 to 100 mg per 100 ml per day. About half of the children with HUS are hypertensive. In a sizable number there are neurological findings such as coma or stupor. It is unclear whether the neurological findings result from a primary central nervous system vasculitis or are a secondary reaction to the fluid overload, azotemia and hypertension. Our experience in California has been more compatible with the latter explanation since the neurological symptoms usually improve quickly after dialysis and administration of antihypertensive drugs. This experience is notably different from the experience in Argentina or in Europe, where a much greater proportion of the patients appear to have primary central nervous system involvement. We have had one patient who was comatose on admission and in whom there were severe central nervous system residua after the renal failure cleared. We assume that central nervous system vasculitis was present in this patient.

The renal histopathology of hemolytic-uremic syndrome is extremely varied. The most typical finding is thrombotic microangiopathy, that is, abnormalities of the small arterioles in the glomerulus. On the other hand, occasionally patients will present with bilateral renal cortical necrosis, with findings of acute tubular necrosis and relatively normal glomeruli, or with proliferative nephritis that in another setting one might call chronic glomerulonephritis.[13] The heterogeneous histopathology may be another reflection of our ignorance about the syndrome. As mentioned earlier, we tend to talk about hemolytic-uremic syndrome as if it is an entity; however, it probably has a number of different causes and these may be related to the different pathologic findings and prognoses.

Prognosis

I would like to comment next on prognosis. In the Stanford series, there were 28 cases of the hemolytic-uremic syndrome in 27 patients. One child had two episodes of HUS separated by one

year during which he seemed to have recovered completely. All of the patients were treated with conservative management of the acute renal failure. Of the 27 patients, there were three deaths, which is an 11 percent mortality rate. It is important to note that two of the three deaths occurred in the five patients seen before peritoneal dialysis was available at Stanford. Thus, of the last 22 patients seen, there was only one death, which is a mortality rate of less than 5 percent. Of the 21 patients who were available for follow-up, 19 were completely well one to eight years after the original episode of hemolytic-uremic syndrome. In two children there was renal insufficiency; in one a transplant was required and in the other there was stable renal insufficiency over a period of a number of years.

Our experience in San Diego has been similar. Of the 13 patients we have seen in the past three years, there have been no deaths. In 11 of the children renal function is now normal. In two, BUN levels are mildly elevated and creatinine clearances are diminished. As mentioned earlier, there is residual central nervous system damage in one. The point is that these patients are terribly ill. They have severe renal failure and without good management would probably die. If they are managed through the acute episode, however, one can expect about 95 percent of the children to survive and 80 to 90 percent to recover completely. The lesson of this is that the management of the acute renal failure of the hemolytic-uremic syndrome is extremely important, because it makes a difference between a dead child and a child with a little or no residual disease. The patient presented today is apparently totally well at the present time. The hematologic features are normal, as are serum creatinine concentration and creatinine clearance. Findings on urinalysis are normal. It is reasonable to expect he will have a perfectly normal life. I repeat, therefore, it is essential that the management of these children during acute renal failure be excellent because of the high probability that good management will provide them with a normal life expectancy.

Management of Acute Renal Failure

It is important then to focus on the management of acute renal failure. In general, there is no specific therapy which will hasten the recovery of renal function in children with acute renal failure. This appears to be true of the hemolytic-uremic syndrome, although we will return to this question later. It is equally true of acute post-streptococcal glomerulonephritis. Therefore, the goal of treatment is to provide the patient time to heal his own kidneys. My approach to this particular problem is utilitarian. By this I mean my therapy is designed to prevent the patients from dying. Table 1 lists the causes of death in children with acute renal failure. The pathogenesis, prevention and therapy of these potentially lethal complications of acute renal failure will be discussed.

TABLE 1.—*Causes of Death in Acute Renal Failure*

1. Circulatory overload
2. Hypertension
3. Electrolyte imbalance, especially hyperkalemia
4. Uremia
5. Infection

The first cause of death to be discussed is circulatory overload resulting in pulmonary edema, peripheral edema, tachycardia and hepatomegaly. The cause of this problem in patients with acute renal failure is salt and water overload resulting from the inability of the kidney to maintain normal body fluid volume and composition. This complication can be prevented by careful regulation of salt and water intake to prevent fluid overload. The treatment of existent circulatory overload is more difficult. The classical forms of therapy for congestive heart failure can be tried. These include phlebotomy, rotating tourniquets, oxygen, bed rest and administration of morphine.

I would like to stress the point that digitalis is contraindicated in patients with acute renal failure. There are two reasons for this. First, in a patient with acute renal failure signs of circulatory overload develop because the heart has been unable to keep up with the excessive load of salt and water and not because there is intrinsic cardiac disease. The heart has increased its stroke volume maximally in an attempt to handle the salt and water overload and this increase has been insufficient to maintain circulatory balance. Digitalis acts primarily by increasing the contractility of the heart. Since patients with acute renal failure have notably increased cardiac contractility, the administration of digitalis is essentially like beating a dead horse. This reasoning would suggest that digitalis is ineffective in patients with acute renal failure, and this is what has been observed clinically. In addition, however, digitalis is highly dangerous in patients with acute renal failure, because it is very easy to induce digitalis intoxica-

tion. Digitalis is excreted by the kidney. Patients with acute renal failure can easily be overdosed with digitalis. This presents a therapeutic dilemma. First, digitalis is poorly dialysable so that it cannot be removed easily. Second, digitalis intoxication is usually treated with intravenously given potassium and this is obviously extremely dangerous therapy for a patient without functioning kidneys. Since digitalis is unlikely to have a positive effect and is very dangerous, it is contraindicated in patients with acute renal failure and no evidence of intrinsic cardiac disease.

What about diuretics? They often do not work in patients with acute renal failure. The reason for this is that diuretics act by decreasing reabsorption of sodium, chloride and water by the nephron. In patients with severe acute renal failure, the glomerular filtration rate (GFR) is often very low. If the GFR is sufficiently low, blocking tubular reabsorption will still not result in urine formation. Thus, diuretics work best in patients with mild acute renal failure and a moderately decreased GFR and least well in patients with severe acute renal failure and essentially no GFR. Nevertheless, in some patients with severe renal failure, diuresis will occur following the administration of a powerful diuretic such as furosemide or ethacrynic acid. A small increase in salt and water excretion can be lifesaving in a patient with severe circulatory overload due to acute renal failure. In addition, powerful diuretics such as ethacrynic acid or furosemide have relatively few side effects. The major reported complication of treatment with these drugs is electrolyte imbalance resulting from an excessive diuresis. This complication would represent a therapeutic triumph in a patient with circulatory overload and acute renal failure. Hearing loss has been reported with both diuretics but this is almost always transient. Since they occasionally work and are relatively safe, I feel the use of diuretics is indicated in patients with circulatory overload due to acute renal failure. Nevertheless, one should not rely upon them to be effective. The ultimate treatment for patients with acute renal failure and circulatory overload is dialysis (either peritoneal dialysis or hemodialysis).

It is worth making a practical point at this time. In general, it takes at least one or two hours to begin a peritoneal dialysis or to organized a hemodialysis. Therefore, when faced with a patient with acute renal failure and circulatory overload, I use oxygen, rotating tourniquets, diuretics and morphine. At the same time, I begin gathering the materials necessary to begin dialysis. By the time it is feasible to institute dialysis, the patient will have either responded to the conservative therapy or not. If not, it is possible to begin dialysis without further delay. We will discuss more about the indications and complications of dialysis in a few moments.

Hypertension in Acute Renal Failure

Next, let us consider the question of the management of hypertension in acute renal failure. About half of the patients with HUS are hypertensive. Hypertension can result in coma, convulsions, encephalopathy and death in these patients. In addition, it can increase the tendency toward circulatory overload by increasing cardiac work. There are several causes of hypertension in patients with HUS. First, in patients with HUS there often are microangiopathic changes of the renal arterioles. Plasma renin activity was measured in five hypertensive patients with HUS and was notably elevated in all five.[14] It seems likely that the renal vascular disease with elevated renin levels can play a significant role in causing hypertension. In addition, the patients have salt and water overload with an increase in extracellular fluid volume which predisposes to hypertension. The prevention of hypertension can be attempted by restriction of salt and water intake. Antihypertensive drugs should be used. Since it is desirable to bring the blood pressure down relatively rapidly, drugs with a rapid onset of action are desirable. In general, I begin therapy with intravenously administered hydralazine but any number of drugs may be used. Propranolol appears to decrease renin secretion and therefore may be useful in these patients. However, the drug has significant cardiac effects and should be used with extreme caution in patients with circulatory overload. Dialysis is an effective way of decreasing the blood pressure because salt and water can be removed, correcting the volume overload.

A third cause of death in patients with acute renal failure is electrolyte imbalance, the most dangerous being hyperkalemia. There are at least three causes of hyperkalemia in patients with acute renal failure: dietary intake of potassium, tissue breakdown and administration of blood. Hyperkalemia can be a particular problem in patients with hemolytic-uremic syndrome. In these patients there is a sizable amount of cellular breakdown in the form of hemolysis. Since the

TABLE 2.—*Treatment of Hyperkalemia*

Agent	*Onset of Effect*	*Duration of Effect*
Calcium gluconate	Minutes	30-60 minutes
Sodium bicarbonate ...	Minutes	1-2 hours
Insulin and glucose ...	20-30 minutes	2-4 hours
Kayexalate	1-2 hours	4-6 hours
Dialysis	Variable	Variable

intracellular concentration of potassium is about 150 mEq per liter, the breakdown of blood releases a sizable load of potassium into the plasma. In addition, the hemolysis is frequently so severe that blood transfusions which tend to exacerbate the hyperkalemia are required.

Preventing Hyperkalemia

The occurrence of hyperkalemia can be prevented in several ways: The dietary intake of potassium should be minimal. A patient should be given at least 20 to 25 percent of his estimated caloric requirement. This has the effect of decreasing protein catabolism, thereby decreasing the breakdown of cells and the release of potassium. Only fresh blood should be used to transfuse children with acute renal failure because the serum potassium concentration rises with the storage of banked blood. The risks of transfusion can be diminished further by using packed red cells rather than whole blood, thereby decreasing the volume of potassium-containing plasma administered. This is also desirable since it diminishes the volume of transfused blood thereby decreasing the risk of circulatory overload. In fact, we often do a partial exchange transfusion in these children. This procedure is done by giving one or two units of packed cells and removing a slight excess of the patient's blood. This procedure will produce a small volume deficit which will tend to decrease the blood pressure and the risk of circulatory overload, while at the same time the number of circulating red blood cells is increased. One should only transfuse these patients with buffy coat poor, washed or frozen red blood cells to diminish the risk of sensitization to tissue antigens in case the patient requires a renal transplant.

In Table 2, the various forms of therapy for hyperkalemia are listed in order of their onset and duration of action. If the patient is severely hyperkalemic with pronounced changes noted on electrocardiograms, the drugs of choice are calcium and sodium bicarbonate. These can reverse electrocardiographic (EKG) abnormalities within one to three minutes, but the effect is short-lived. Calcium acts by antagonizing the effect of potassium on cardiac muscle. Sodium bicarbonate administration causes release of hydrogen ions from the cells in exchange for potassium ions. If the hyperkalemia is less severe or an emergency situation has been temporarily alleviated by calcium and sodium bicarbonate administration, the next form of therapy is insulin and glucose. Insulin increases the uptake of glucose by cells and potassium is taken up with the glucose. It is essential that glucose be given to cover the insulin infused or the patient can become symptomatically hypoglycemic. It is said that insulin and glucose begin to act in 20 to 30 minutes, but I have seen EKG changes sooner. The effect lasts only a few hours. Calcium, sodium bicarbonate, and insulin and glucose do not remove potassium from the body. Therefore, hyperkalemia tends to recur relatively rapidly. There are two forms of therapy that do remove potassium from the body. The first is the ion exchange resin sodium polystyrene sulfonate (Kayexalate®), which is given in the sodium form either orally or rectally. The resin exchanges sodium for potassium and the potassium loaded resin is excreted in the stools. This has the disadvantage that patients with acute renal failure can get an excessive load of sodium by the use of Kayexalate. A second method for removing potassium is peritoneal dialysis or hemodialysis.

Uremia and Infection

A fourth cause of death in acute renal failure is uremia. A number of problems fall into this category, but the primary life threatening aspects are neurologic symptoms, including coma, stupor and convulsions. These symptoms can also be caused by hypertension or by central nervous system vasculitis. There are a variety of nitrogenous products which build up in the blood stream of patients with acute renal failure. Although the correlation between the concentration of any of these products and the occurrence of neurologic symptoms is poor, it is generally assumed that some product (or products) of protein metabolism is responsible for the neurologic symptoms. The onset of neurologic symptoms and the rise in the concentrations of urea and creatinine can be slowed by giving enough calories to diminish protein catabolism. The symptoms of uremia can often be treated or prevented by dialysis. As I mentioned earlier, the BUN level can rise at an extremely rapid rate in patients with hemolytic-

uremic syndrome because of the massive red blood cell breakdown. Therefore, in patients with HUS dialysis should be done relatively early in order to avoid extremely elevated blood levels of urea and other protein breakdown products.

The fifth cause of death in acute renal failure is infection. Several things tend to make a patient with acute renal failure more susceptible to infection. First, patients with uremia appear to have a decreased resistance to infection. Second, these patients are frequently immobile and therefore there is a tendency for hypostatic pneumonia and decubiti to develop. Third, it is a common practice to monitor urine output of these patients by the use of indwelling catheters. The risk of infection can be decreased by careful nursing, including strict attention to such things as turning, coughing and deep breathing. In addition, the use of indwelling bladder catheters is unwarranted. The only information which a catheter provides is an hour by hour measurement of the urine output. This information is essentially worthless. Therapeutically it is important to know whether a small or a large volume of urine is being produced. This information becomes available quickly because the patient either voids or an enlarged bladder develops if the urine volume is high. An indwelling catheter in a patient with a low urine output and decreased resistance to infection is an invitation to infection. The treatment of infection in patients with acute renal failure is similar to that of other patients, namely the use of the appropriate antibiotics. Of course, some antibiotics must be given in reduced doses to patients with impaired renal function. It is important to recognize that in many series, 50 percent of the deaths in acute renal failure are from infection, and therefore one must have a very high index of suspicion.

The indications for dialysis in a patient with acute renal failure are circulatory overload, severe hypertension, severe electrolyte imbalance and symptoms of uremia. These indications are virtually identical with the causes of death in acute renal failure. The implication of this is that dialysis should be done promptly in every patient with acute renal failure who responds poorly to conservative measures. Dialysis, whether peritoneal dialysis or hemodialysis, is a relatively benign procedure and is frequently lifesaving in patients with acute renal failure. The choice between peritoneal dialysis and hemodialysis depends more on the experience of the physician doing the procedure and the available equipment than on any advantage of one over the other. One possible complication of hemodialysis is probably worthy of mention. This is the dialysis dysequilibrium syndrome. This syndrome can occur if the serum osmolality is lowered too rapidly. This tends to occur in patients in whom BUN is notably elevated before dialysis. The complication can be prevented by increasing the osmolality of the dialysis bath, thereby decreasing the rate of fall of the serum osmolality.

Use of Anticoagulants

No discussion of the hemolytic-uremic syndrome would be complete without mention of the use of anticoagulants, particularly heparin. A number of uncontrolled studies have suggested that heparin is valuable in the treatment of the hemolytic-uremic syndrome.[2-4] These observations were made in California, and the conclusion was reached by comparing the results obtained with those obtained without heparin in Argentina. When heparin treated patients are compared with the patients from Stanford who received no heparin, no difference is seen.[1] In addition, a recent controlled study of the use of heparin in Argentina indicated that there was no improvement in the prognosis following the use of heparin.[15] In general, it would appear that the prognosis of patients with the hemolytic-uremic syndrome in California treated conservatively is so good that it is difficult to justify a therapeutic trial of a potentially dangerous drug such as heparin. This opinion is not universally held, and a recent report suggests that heparin may have increased the world-wide survival rate of patients with HUS. This report suggests an international collaborative study to answer the question.[16]

More recently, the use of streptokinase has been proposed.[17-20] The rationale of this therapy is that thrombi can be seen in the small vessels of patients with hemolytic-uremic syndrome. It is felt that streptokinase might hasten the removal of these thrombi and therefore improve the prognosis. Once again, however, this is proposing the use of a potentially dangerous drug in a group of patients whose prognosis is excellent without the drug.

In conclusion, the hemolytic-uremic syndrome in California appears to be significantly different from the syndrome described in Argentina and Europe. In California, the illness is characterized by a severe gastrointestinal prodrome which is

followed by acute renal failure and hemolytic anemia. The prognosis is excellent with 95 percent of the patients surviving the acute illness and about 90 percent recovering normal renal function. For this reason, intensive medical management of the acute renal failure is mandatory.

REFERENCES

1. Tune BM, Leavitt TJ, Gribble TJ: The hemolytic-uremic syndrome in California—A review of 28 nonheparinized cases with long-term follow-up. J Pediatr 82:304-310, Feb 1973
2. Lieberman E, Heuser E, Donnell GN, et al: Hemolytic-uremic syndrome. N Engl J Med 275:227-236, Aug 4, 1966
3. Lieberman E: Hemolytic-uremic syndrome. J Pediatr 80:1-16, Jan 1972
4. Piel CF, Phibbs RH: The hemolytic-uremic syndrome. Pediatr Clin North Am 13:295-314, May 1966
5. Gianantonio C, Vitacco M, Mendilaharzu F, et al: The hemolytic-uremic syndrome. J Pediatr 64:478-491, Apr 1964
6. Gianantonio CA, Vitacco M, Mendilaharzu F: The hemolytic-uremic syndrome. Proc 3rd Internat Congr Nephrol, Washington 1966, Basel/New York 1967, S Karger AG, Vol 3, pp 24-36
7. Gianantonio CA, Vitacco M, Mendilaharzu F, et al: The hemolytic-uremic syndrome—Renal status of 76 patients at long-term follow-up. J Pediatr 72:757-765, Jun 1968
8. Berman W: The hemolytic-uremic syndrome: Initial clinical presentation mimicking ulcerative colitis. J Pediatr 81:275-278, Aug 1972
9. Bar-Ziv J, Ayoub JIG, Fletcher BD: Hemolytic-uremic syndrome: A case presenting with acute colitis. Pediatr Radiol 2: 203-206, Aug 1974
10. McLean MM, Jones CH, Sutherland DA: Haemolytic-uraemic syndrome. A report of an outbreak. Arch Dis Child 41: 76-81, Feb 1966
11. Mettler NE: Isolation of a microtatobiote from patients with hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura and from mites in the United States. N Engl J Med 281: 1023-1027, Nov 6, 1969
12. Tune BM, Groshong T, Plumer LB, et al: The hemolytic-uremic syndrome in siblings—A prospective survey. J Pediatr 85: 682-683, Nov 1974
13. Aschinberg LC, Bennett B, Edelmann CM, et al: The heterogeneous pathology of the hemolytic-uremic syndrome. Pediatr Res 7:408, Apr 1973
14. Powell HR, Rotenberg E, Williams AL, et al: Plasma renin activity in acute poststreptococcal glomerulonephritis and the haemolytic-uraemic syndrome. Arch Dis Child 49:802-807, Oct 1974
15. Vitacco M, Avalos JS, Gianantonio CA: Heparin therapy in the hemolytic-uremic syndrome. J Pediatr 83:271-275, Aug 1973
16. Proesmans W, Eeckels R: Has heparin changed the prognosis of the hemolytic-uremic syndrome? Clin Nephrol 2:169-173, Sep/Oct 1974
17. Bergstein JM, Edson JR, Michael AF: Fibrinolytic treatment of the haemolytic-uraemic syndrome. Lancet 7:448-449, Feb 19, 1972
18. Monnens L, Kleynen F, van Munster P, et al: Coagulation studies and streptokinase therapy in the haemolytic-uraemic syndrome. Helv Paediat Acta 27:45-54, Apr 1972
19. Winterborn MH, White RHR, Stuart J: Fibrinolytic treatment of the haemolytic-uraemic syndrome. Lancet 1:1071, May 13, 1972
20. Van Wieringen P, Monnens L, de Jong M: Follow-up of 62 children with hemolytic-uremic syndrome treated by streptokinase. (Abstract) Kidney Internat 7:363-364, May 1975

Adolescent Menstrual Disorders

I want to know whether there is an important abnormality here or not. If there is not, I am confident that I can pinpoint the emotional precipitating cause for hypothalamic pituitary suppression. I do nothing—and, when I say nothing, I do not mean absolutely nothing. I sit down and talk to this patient for some time, explaining to her that, in my view, not menstruating is not, per se, doing her any harm. I believe that most patients who are amenorrheic for this reason are not at risk simply because they are not menstruating. I seldom find it necessary to produce any kind of withdrawal bleeding to raise their morale. It is my experience that patients accept an explanation of this kind. They come because they want to know if something is the matter with them; and I generally do nothing except give them this kind of explanation. Now, I do not lose track of them completely; I see them at intervals. I might even begin by bringing them back in six months, but I will probably see them yearly after that because, otherwise, I think they lose faith in what you have told them. They say, "Well, I wonder if he really understood what he was talking about," and they go off to another department and do the whole thing again—which is, generally speaking, unnecessary.

—C. J. DEWHURST, MD, *London*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 22, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Pericarditis—Medical Staff Conference, University of California, San Francisco. West J Med 123:467-476, Dec 1975

Pericarditis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SCHMID:* *The speaker today is Dr. Mervin J. Goldman, Professor of Medicine and one of our outstanding cardiologists, who will talk on the subject of pericarditis.*

DR. GOLDMAN:† Thank you Dr. Schmid. I would like to begin by defining pericarditis. Pericarditis is an inflammatory disease, not necessarily infectious, which involves not only the pericardial surfaces but in most instances the epicardial surface of the heart. Therefore, I think a more proper term for an understanding of the disease is epicarditis. One should appreciate that commonly there is involvement of the pleural surfaces as well as the pericardial surface. In most instances, the involvement is epicardial but it is very difficult or impossible at times to determine the depth of penetration of the inflammatory process into the myocardium. In some patients the disease is not limited to the epicardial surface but involves the entire myocardium with a much more serious prognosis. It is likely that in some of these patients the condition progresses into a chronic myocarditis which we recognize and loosely call cardiomyopathy.

In addition, we know that in many of these patients, probably all of them to a greater or lesser degree, pericardial effusion is present. A common characteristic feature of this whole group of diseases is the tendency to relapse. The disease process over the course of months to years, can go on to constriction or the pericardial effusion can progress into a seroconstrictive phase; that is, the clinical feature is that of constriction but there are still loculated areas of pericardial effusion. Both of these require surgical therapy (Figure 1).

In order to get some concept of the cause of the disease process, I have prepared Table 1. What does the physician think of when he makes the diagnosis of pericarditis? A whole host of possible causes comes to mind.[1,2] Probably the most common, is the so-called viral or idiopathic type. The term idiopathic is used because no other obvious cause is uncovered. The assumption is that it is viral but unless one has excellent viral laboratory facilities, it is not too common to

*Rudi Schmid, MD, Professor of Medicine.
†Mervin J. Goldman, MD, Professor of Medicine.

TABLE 1.—*Acute Pericarditis*

1. Infectious
   (a) Viral (idiopathic): Coxsackie, influenza, etc.
   (b) Bacterial: Tuberculosis, Staphylococcus, Streptococcus, pneumococcus, meningococcus and so forth
   (c) Fungal
   (d) Parasitic
2. Hypersensitivity
   (a) Collagen diseases: Rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus
   (b) Following myocardial infarction: Dressler's syndrome
   (c) Postpericardiotomy
   (d) Trauma: blunt or penetrating
   (e) Serum sickness
   (f) Drug reaction
   (g) Idiopathic (viral) relapsing
3. Metabolic
   (a) Uremia
   (b) Myxedema
4. Neoplasm
5. Dissecting aneurysm of aorta
6. Myocardial infarction
7. Cobalt-beer myocardiopathy
8. Radiation therapy

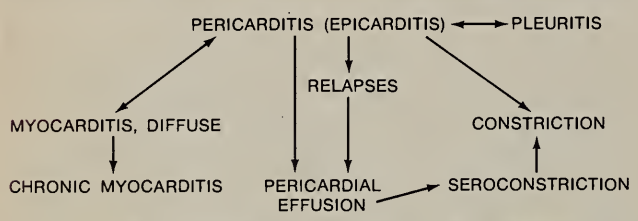


Figure 1.—Spectrum of pericardial disease.

identify a specific virus. Considerable attention has been paid to the Coxsackie virus in recent years, but almost any virus known to mankind can be associated with this pericarditic process. Examples are the influenza virus, enteroviruses, ECHO viruses, infectious mononucleosis and, in the days when the disease was more prevalent, poliomyelitis.

Bacteria may invade the pericardial surface secondarily. Tuberculosis[4] is the one major consideration that I will be speaking about today, but all of the other pyogenic organisms[3] (Staphylococcus, Streptococcus, pneumococcus, meningococcus and so forth) can and do involve the pericardial surface. Fungal disease can do it. Even though we commonly see coccidioidomycosis in the state of California, the incidence of clinically recognized pericarditis is uncommon. We have occasionally seen in this area some cases of constrictive pericarditis secondary to histoplasmosis. Parasitic disease may do this; toxoplasmosis can cause acute pericarditis and myocarditis, and amebiasis on rare occasions can do it.

I would like to illustrate the latter with a patient whom I saw many years ago. This was a 45-year-old man who had never been out of the state of California (Figure 2). He had had complaint of severe pain in the right lower chest and right upper abdomen for about one month associated with high spiking fevers, and then ascites and peripheral edema developed. He presented with the typical findings of pericarditis and tamponade and, in addition, the liver was extremely tender with pronounced elevation of the right

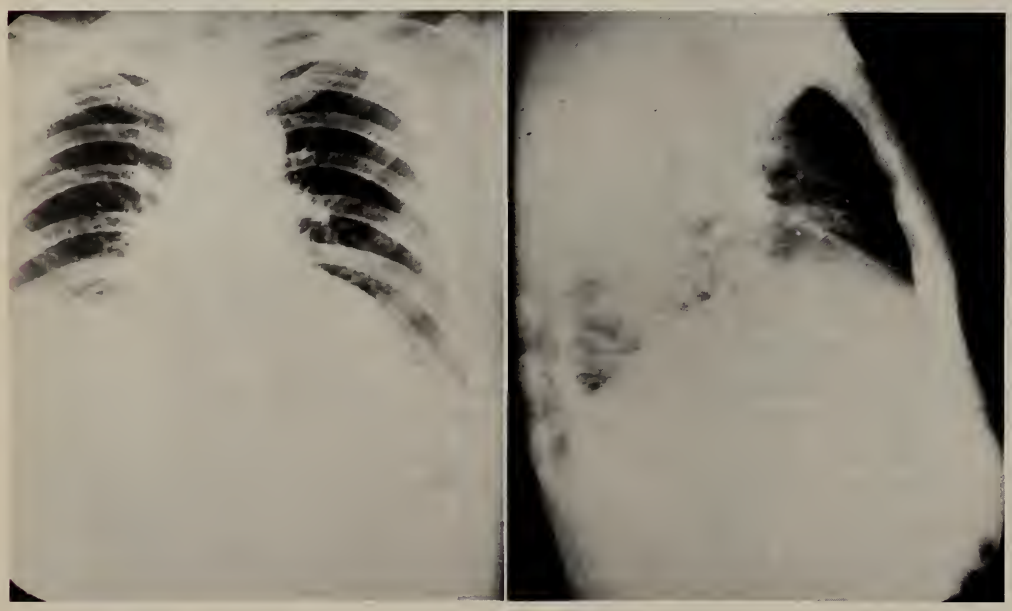


Figure 2. — Posteroanterior and lateral x-ray studies of chest in patient with amebic liver abscess and amebic pericarditis.

hemidiaphragm in the central portion. This patient had amebiasis, as proven by aspiration of the liver abscess, and went on to complete recovery on antiamebic therapy alone.

Then we have a whole host of diseases that we may list as hypersensitivity diseases that involve the pericardial surface: Pericarditis is common in acute rheumatic fever as part of a more generalized pancarditis, and rheumatoid arthritis is known to have a high incidence of pericarditis, at least as found at autopsy. Pathologists have been telling us for many decades that adhesive pericarditis is a very common finding at autopsy in patients who have suffered from chronic rheumatoid arthritis. Clinically, it is not commonly recognized. Systemic lupus erythematosus is commonly manifest by pericarditis.

Following myocardial infarction one can see features that are clinically indistinguishable from viral or idiopathic pericarditis.[5] Typically, the patient is three or more weeks post-myocardial infarction and becomes ill with chest pain associated with fever, pericardial friction rub and, very commonly, involvement of the pleural surfaces as well (Dressler's syndrome). This is probably an autoimmune disease in some way related to the previous myocardial infarction.

A similar process is seen and has been labeled the post pericardiotomy syndrome. In the early day of closed mitral valve surgical procedures, it was thought that one was seeing exacerbation of rheumatic disease. However, this has since been disproven and we appreciate that, again probably through autoimmune mechanisms, a patient in whom surgical operation on the heart has been carried out and the pericardium opened may have subsequent episodes of pericarditis.

Trauma, whether it be blunt or penetrating, can set up an inflammatory process beginning with hemopericardium and produce features that are indistinguishable from those of idiopathic or viral pericarditis. This process also has a tendency to relapse. In the days when horse serum was commonly used, pericardial disease, with pericardial effusion, was not a rare finding in association with the clinical features of serum sickness. Drug reactions may also produce these features. The most common that we are aware of is that related to hydralazine with the lupus syndrome, but on rare occasions other drugs, even penicillin, can induce the serum sickness-like illness associated with pericarditis.

Another feature of idiopathic or viral disease is the tendency to relapse. Relapsing pericarditis is likely not due to repeated episodes of viral infection, but is rather due to superimposed autoimmune disease.

I would like to turn to a discussion of pericarditis related to metabolic disorders. Before renal dialysis and renal transplantation, uremic pericarditis was seen not uncommonly but this was not a major therapeutic problem because this occurred in the end stage of the disease and there was no available therapy. Now, when we can keep people living comfortably for years with dialysis or renal transplantation, the recognition and treatment of uremic pericarditis becomes of major importance, and one can no longer neglect this important complication. Effusion, tamponade and constriction may occur and these must be treated in conjunction with dialysis to salvage the patient.[6]

Myxedema is commonly associated with pericardial effusion and may go unrecognized, especially in elderly patients thought to be in congestive heart failure for obscure reasons. Unless myxedema is brought to mind by the clinical features of the disease and then pericardial effusion looked for, it can be easily overlooked. Remember that part of the cardiovascular problem, and so-called congestive heart failure that one sees in myxedema, need not be myocardial but rather pericardial effusion with tamponade.

Neoplasm can involve the pericardial surfaces and myocardium. Most commonly this is seen as a secondary response to other malignancy, most commonly bronchogenic carcinoma and lymphomas—but any malignancy that can involve the chest and mediastinum can spread and involve the pericardial and myocardial surfaces. I can recall a patient that I discussed on rounds here about five years ago, who was a young man presenting to the Moffitt emergency room with a complaint of bleeding hemorrhoids. The next thing he knew he was in the coronary care unit because the physician on duty was very conscientious, did a complete physical examination and detected a pericardial friction rub. At that time the patient was relatively asymptomatic in relation to the pericardial disease and the cause of this was unknown. The patient's condition rapidly deteriorated and he died. At autopsy, a primary sarcomatous lesion of the paricardium was noted.

Dissecting aneurysm of the aorta can involve the pericardial surface by retrograde dissection and leakage of blood into the pericardial space.

In most instances we think of this as a terminal event. However, this is not invariably true. There may be a little leakage of blood, enough to cause pain and a pericardial friction rub, and yet not sufficient to result in tamponade and death. If recognized early an occasional patient can be saved with surgical operation.

The pericarditis associated with acute myocardial infarction is well known and need not be discussed. The cobalt beer myocardiopathy was an interesting entity, one that I discussed here at Grand Rounds a few years ago. This was an iatrongenic disease that was seen in 1965 and 1966 in which congestive heart failure abruptly developed in patients and cardiomegaly was present. It occurred in persons who were heavy beer drinkers at a time when some beer companies introduced cobalt into beer to give it better foaming qualities. One interesting feature of this disease process was the high incidence of significant pericardial effusions. Removal of pericardial fluid, however, in no way helped these patients because the pericardial effusion was not the major cause of the hemodynamic deterioration.

Radiation therapy does produce damage to the pericardium and can lead to acute episodes of pericardial reaction, pericardial effusion and even later on pericardial constriction.

I will now review the clinical manifestations of the disease. The clinical spectrum may extend from asymptomatic persons to ones who are desperately ill. Occasionally one may see a person who has had a respiratory infection or gastroenteritis, and on physical examination a pericardial friction rub is heard. The patient may be entirely asymptomatic and in a day or two the rub is gone. I strongly suspect that acute pericarditis, and I think this is also true for acute myocarditis, is a very common disease but we only recognize those cases of sufficient severity to come to our attention—and the great majority of them are never diagnosed and fortunately never cause any clinical harm.

The usual history that one obtains in these persons is that of a preceding respiratory influenza-like illness, or a gastroenteritis. Then fever develops and substernal chest pain of a pleuritic nature that is definitely aggravated by inspiration, by motion of the chest and at times by swallowing; the pain is worse with the patient lying supine and is relieved to some degree by sitting up. There may be associated symptoms related to pleuritis since pleural involvement is a very common accompaniment.

The physical signs one sees are largely related to the disease process per se and the hemodynamic consequences of them. The sine qua non is the pericardial friction rub. Classically, there are three phases: atrial systole, ventricular systole and ventricular diastole. However, on occasion one may hear only a two component rub, especially if fibrillation is present. The major problem arises in the patient in whom one hears only a single component rub, say only in systole, and there may be a problem at any given moment in deciding if this is a rub or a murmur. This requires repeated observation because typically these rubs change or come and go from moment to moment.

Atrial arrhythmias are reasonably common because of the involvement of the thin walled atrium. Usually these are not clinically serious. Commonly one sees atrial ectopic beats, but on occasion runs of other atrial tachyarrhythmias may occur.

The other signs of pericarditis are related to the hemodynamic sequelae of the disease and these fall into three categories. The first involves the question of whether the disease is limited to the pericardial-epicardial surface, or is a more diffuse myocarditis in which one sees cardiac dilatation and ventricular failure. If this is so, the prognosis is much more ominous. The second hemodynamic consequence of the disease is pericardial effusion and the third is constriction.

The degree of hemodynamic change that results from pericardial effusion is related to the rapidity with which the fluid develops. In those instances in which fluid or blood accumulates in the pericardial sac within minutes, as may occur with cardiac rupture or secondary to ventricular puncture, the accumulation of as little as 150 ml of blood is enough to cause cardiac tamponade and even death. On the other hand, if the fluid accumulates over the course of days or weeks, or longer, the pericardial sac can gradually dilate and contain over a liter of fluid, and the patient need not be in acute tamponade. However, there comes a critical level when the pericardial pressure becomes so high that filling of the heart is impaired and, therefore, output is critically reduced.

What are the signs we look for to recognize this significant degree of significant pericardial effusion? The two most common signs are Kussmaul's

sign on the venous side and the paradoxical pulse on the arterial side. Under normal situations when anyone takes a deep breath, intrathoracic pressure falls and all structures within the thorax have a more negative pressure including the venous system. Normally as one observes the neck veins during inspiration the venous pressure falls. However, in a patient in whom there is significant pericardial effusion or constriction, the right heart cannot accept this increased venous flow, and this pressure is transmitted into the right atrium and up into the neck veins so one sees an actual elevation, or on a more subtle level no change in the venous pressure with inspiration. However, one has to remember that this is by no means pathognomonic for pericardial effusion. One will see exactly the same phenomenon in those persons with a notably dilated and noncompliant right ventricle and in patients with obstructive lung disease because of the high intrathoracic pressure. We can, of course, produce this at will iatrogenically when we use positive pressure ventilation.

The paradoxical pulse is really a misnomer. It is not paradoxical at all, it is merely an accentuation of the normal phenomenon. With inspiration there is normally a small fall in systolic blood pressure of up to 10 mm of mercury. In the so-called paradoxical pulse there is accentuation of the normal; that is, there is more than a 10 mm fall in systolic blood pressure with inspiration. This is due to the alteration of hemodynamics within the chest cavity. In a normal person left heart pressures and pulmonary venous pressure will fall with inspiration along with the fall in intrathoracic pressure. However, with pericardial effusion or with constriction, the pressure within the cavity of the left ventricle will remain unchanged as the pressure within the thorax falls. Actually there may be an elevation of intrapericardial pressure because of the continuum of the parietal pericardium to the diaphragm and, with inspiration, the downward movement of the diaphragm tenses the pericardium and increases the intrapericardial pressure. As a result, one sees a normal fall in pulmonary venous pressure with inspiration, without a fall in left heart pressure. Therefore, there is a change in gradient which reduces inflow of blood into the left ventricle resulting in a fall in stroke output, and therefore a fall in systolic blood pressure. How helpful is the laboratory in telling us the cause of the patient's pericarditis? Most of my discussion now will center upon the two major points of differential diagnosis: idiopathic or viral versus tuberculous pericarditis.

In most of the other causes there will be some clue from history, physical examination or routine laboratory work to suggest the disease process. Aspiration of pericardial fluid or pleural fluid may help in differentiating between viral and tuberculous disease. Both fluids are exudative, and have a high number of mononuclear cells. The presence or absence of tubercle bacilli is critical. The yield from smears of aspirated pericardial fluid is low; in one third to one fourth of the cases one can find the organism on smear.

One has a slightly better chance using culture, but again this is by no means 100 percent accurate. So negative organisms on smear, coupled with a significant delay in culture results, implies that tuberculosis is difficult to exclude. A tuberculin skin test can be exceedingly helpful, for in most instances findings on a tuberculin skin test are positive. One must consider the possibility of overwhelming tuberculous infection in those patients on corticoid or immunosuppressive therapy, or who are immunosuppressed because of their basic disease, for whom negative results on a skin test are common.

An electrocardiogram is helpful in establishing or confirming the diagnosis. What is seen on an electrocardiogram is not due to pericardial disease per se but due to the associated epicarditis. Classically one sees diffuse ST segment elevation followed over the course of days to weeks with return of the ST to the isoelectric line and T-wave inversion and then, in most instances, return to normal. It is important to emphasize that one does not see abnormal Q waves, interventricular conduction defects or atrioventricular conduction defects in the syndrome that we call pericarditis. If the latter are seen, other disease is present—either coronary artery disease or a more diffuse myocarditis.

It has been very helpful to me to utilize electrocardiograms in a negative sense. There is one common disease associated with pericarditis in which one does not see these typical electrocardiographic changes, and that is uremic pericarditis. The disease process does not involve enough epicardial myocardium to produce the electrocardiographic events. The pericardial disease is limited to the pericardium and this does not reflect itself electrocardiographically. This has been helpful to me and I can illustrate it by two

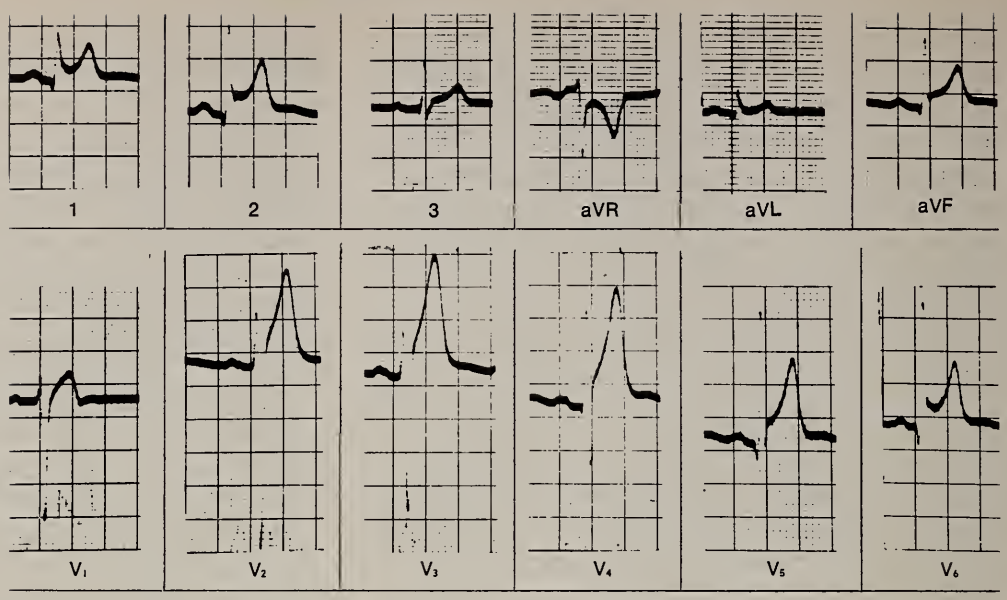


Figure 3.—Electrocardiogram illustrating diffuse ST elevation in a patient with pericarditis.

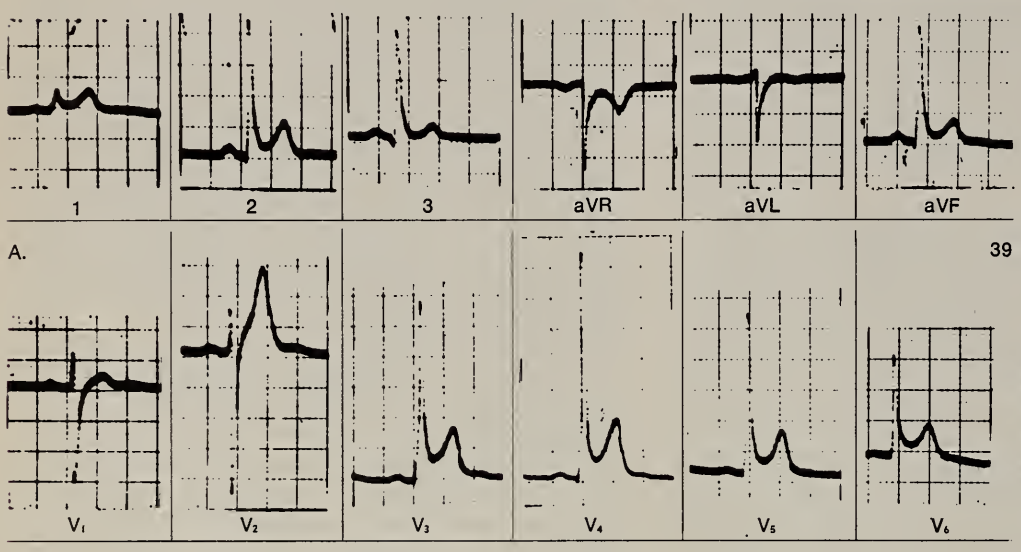


Figure 4.—Electrocardiogram illustrating ST elevation and T-wave inversion in pericarditis.

cases I have seen in the last couple of years. These patients were uremic. They presented to the hospital on their final admission with chest pain and loud pericardial friction rubs. The initial diagnosis was uremic pericarditis. However, in both of these patients pronounced ST segment elevation in various leads was noted which made one very suspicious that the disease was not uremic pericarditis. Both of these patients died and at autopsy acute myocardial infarction was found. I think it is well to remember that if one is dealing with uremic pericarditis one should not expect to see the usual ST-T wave changes.

In the tracing shown in Figure 3 one sees ST segment elevation in all leads except AVR, as evidence of an acute current injury involving the entire epicardial wall. In Figure 4 is a similar electrocardiogram in a normal person.[8] One sees ST elevation which simulates pericarditis, but was a normal variant in this case. To aid in this difficult differential diagnosis one can exercise the patient and, at least in my experience, the ST segments return to the isoelectric line in a normal person (Figure 5). Figure 6 is a later stage of pericardial disease in which there is still some ST elevation but now one sees the diffuse T-wave inversion that is evidence of diffuse epicarditis. The electrocardiogram in Figure 7 illustrates the phenomenon of electrical alternans. With the one exception of paroxysmal supraventricular tachycardia, the presence of an electrical alternans is indicative of significant heart disease. The most common disease that we see in adult practice that causes this is pericardial effusion. The one lesson to learn is if you have not suspected pericardial effusion before and you note sinus rhythm and electrical alternation, go back to the patient and reevaluate for this possibility.

X-ray studies may or may not be of value. With minimal effusion one can see a normal cardiac silhouette. The major problem arises in distinguishing between pronounced cardiac dilatation and pericardial effusion which may be impossible by conventional radiology. In former days we had various techniques of carbon dioxide (CO_2) and dye injections to study these patients, but fortunately now we have a very simple noninvasive technique by which we can certainly diagnose the presence of significant pericardial effusion and that is echocardiography.

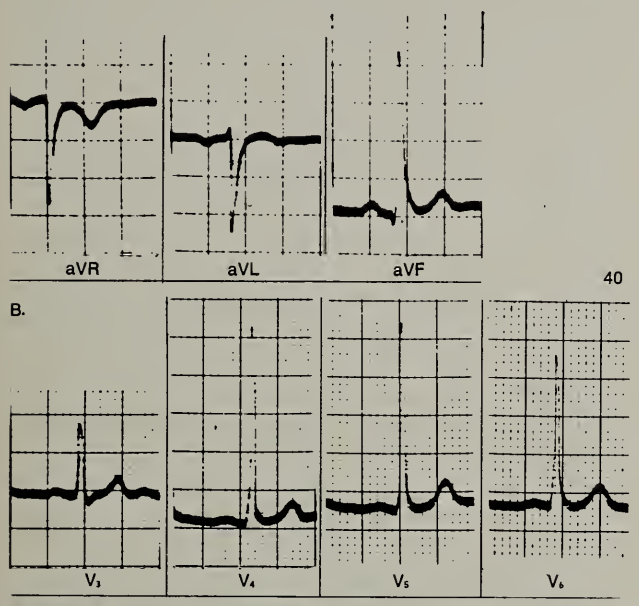


Figure 5.—Electrocardiogram of a normal young man.

Pericardiocentesis is indicated in at least two circumstances: One is for treatment of tamponade and the other is for diagnosis. Unless the tap is urgently necessary I would strongly advise that it be done either in a cardiac catheterization laboratory or in an intensive care unit where similar facilities are available. This will permit one to make measurements of intrapericardial pressure and simultaneous right heart pressures, or at least central venous pressure. One can thereby gain diagnostic and prognostic information. If as the intrapericardial pressure falls with removal of fluid, the right atrial pressure falls concomitantly, one can be confident that the hemodynamic problem in that patient is the pericardial effusion. On the other hand, if the right atrial pressure remains elevated, as the intrapericardial pressure falls, it indicates that serious diffuse myocardial disease is present and the pericardial effusion is not a major hemodynamic problem or that one is dealing with the entity of so-called seroconstriction where there are already fibrous or fibrinous adhesions within the pericardial sac. If the fluid is loculated, surgical operation is indicated.

In a situation in which we know pericarditis is

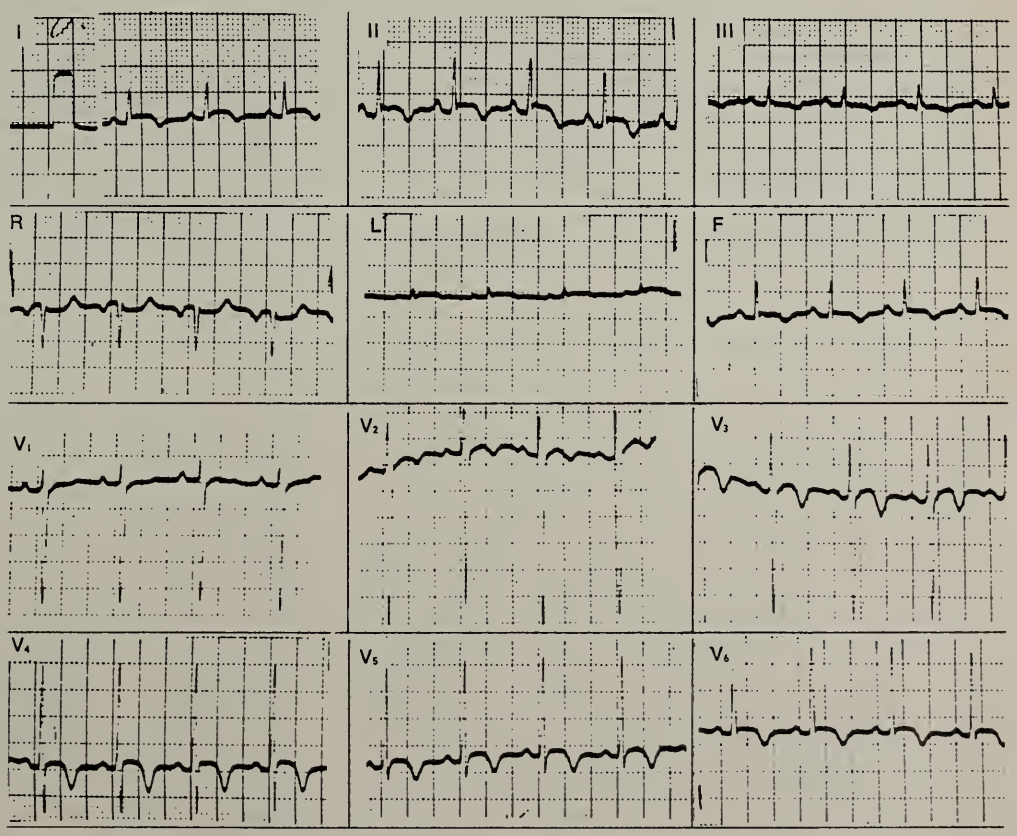


Figure 6.—Electrocardiogram of same person as in Figure 5 following exercise.

present and there is no other obvious cause, we are often left with the two major points of differential diagnosis. That is, is it viral or idiopathic, or could it be tuberculosis? The absence of obvious tuberculous disease on an x-ray study of the chest, or in any other organ, by no means excludes the diagnosis. A tuberculin skin test, as I mentioned before, is exceedingly helpful. If it gives positive findings, it does not prove the existence of tuberculous pericarditis. It is very important to establish or rule out the diagnosis of tuberculosis since, if it is tuberculosis, the patient is faced with a considerable mortality, not only from the tuberculous involvement of the pericardium but other organs in the body. Secondly we know that the earlier the patient is treated with chemotherapy for tuberculous pericarditis the less will be the likelihood of constriction in the future that will require surgical intervention.

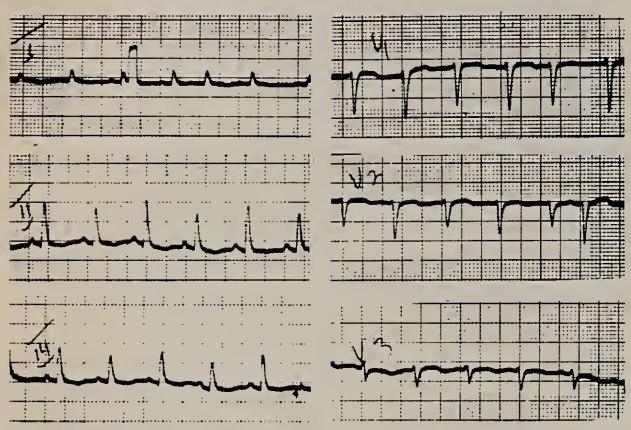


Figure 7.—Electrocardiogram illustrating electrical alternans in a patient with pericardial effusion.

Studies that Dr. Emile Holman did many years ago show that if a patient was treated within a month of the onset of illness with antituberculosis therapy, the need for subsequent pericardectomy was very small, well under 5 percent. On the other hand, if the disease process was present for

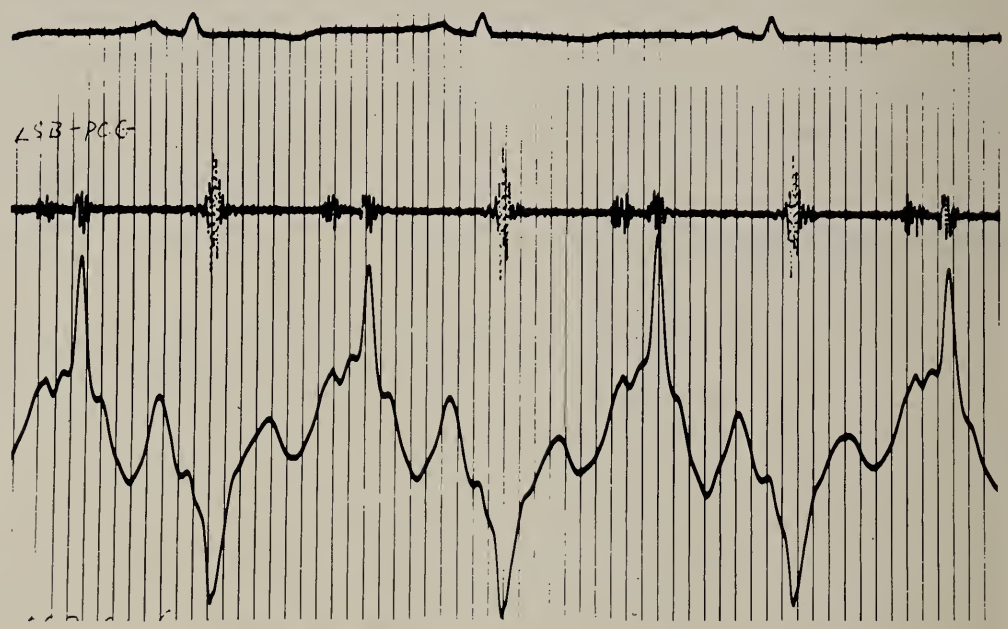


Figure 8.—Electrocardiogram, phonocardiogram and displacement cardiogram in a patient with constrictive pericarditis.

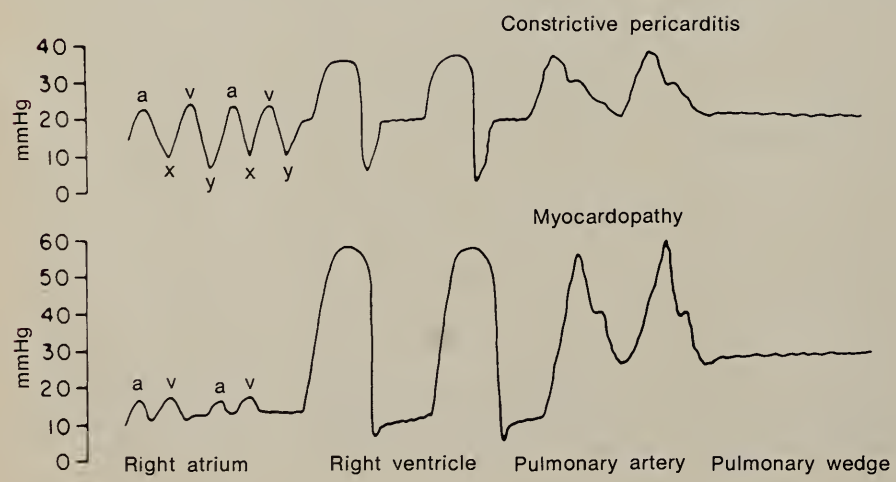


Figure 9.—Cardiac pressures in myocardial and pericardial disease.

more than three months it was very likely that he would require pericardectomy in the future.

What does one do when one has run the gamut of the tests available to us, one has even examined the pericardial fluid and one is reluctant to wait four or more weeks for results of cultures—fully realizing even if the culture results are negative this will not completely exclude the diagnosis? This is an indication for open surgical biopsy, and when one does this will have to be left to the judgment of the physician and the clinical course of the patient. In general, I would like to advise the following: If the patient is still acutely ill, febrile and with evidence of active disease as evidenced by rub and effusion for three weeks and the diagnosis is still not established, and tuberculosis is a possibility, an open pericardial biopsy is indicated. The risk of such is generally very minimal. It can be done, if need be, under local anesthesia and one can obtain an adequate specimen of tissue for pathological and bacteriological study.[7] If present, in all probability the diagnosis will be made on pathological examination permitting the physician to start immediate antituberculous therapy. If the physician wants to be a little more cautious, he could start antituberculosis therapy empirically a few days before the surgical procedure.

Viral or idiopathic pericarditis is often a diagnosis of exclusion. In my opinion, there is no specific therapy for this particular entity. The treatment is purely symptomatic and includes treating the complication of tamponade. Aspirin is probably the most effective therapy we have. It is a good anti-inflammatory agent, it does reduce the fever and the symptoms of the disease. There is no doubt that corticoids will do the same thing and even more dramatically. However, I would strongly advise against the routine use of corticoids because so often I feel that I have a bull by the tail. The patient is begun on corticoid therapy, assuming one has reasonable assurance that one is not dealing with tuberculosis or some other pyogenic disease, and the patient promptly gets better. But when one starts to taper the corticoids or reduce them to zero the disease process recurs. There are instances, and I remember Dr. Freedberg commenting on this also, in which patients have been forced to remain on corticoids for years because whenever the corticoid therapy was reduced or discontinued the disease process reappeared. I would therefore advise you not to use corticoids unless you are dealing with a serious, life-threatening disease.

What is the prognosis of this entity of idiopathic or viral pericarditis? So often it has been termed benign, and in most instances it is. However, there are two significant features of the disease: As has been discussed, tamponade may occur and if it goes unrecognized and untreated, can be fatal. The second complication is recurrence and relapse. This is likely an autoimmune phenomenon rather than continuing or recurring viral disease. I personally refrain from giving corticoids here also because I have difficulty in getting patients off the drug once they are on it. The final complication, of course, is constriction, or seroconstriction, in which surgical operation is the only treatment.

There is one physical finding in constrictive pericarditis that may be confusing. I recall one instance a few years ago when one of our house staff asked me to see a patient whom we knew had constrictive pericarditis. That is, he looked at an x-ray film of the patient and there was a rim of calcium encasing the entire heart, and all of the clinical findings were present in the patient except, he stated, there was a right ventricular lift. It was true as one looked and felt the precordium that there was a very prominent pulsation along the left parasternal region except this pulsation was in early diastole and not a systolic pulsation. The reason for this is reasonably obvious as you think about it. One is dealing with a situation in which the whole heart is encased in a rigid sac. With early diastole and the rush of blood into the ventricles the whole heart is thrust up against the chest wall and this is what one feels. In Figure 8 one can see this well illustrated with a displacement cardiogram placed over the parasternal region, and we can notice in early diastole the very pronounced anterior pulsation which can be seen and felt and is simultaneous with the early sound in diastole. This is the pericardial knock.

At times it may be exceedingly difficult to differentiate between the entity of restrictive myocardial disease and constrictive pericardial disease. One is faced with a patient in whom there is a normal sized heart or minimal cardiomegaly judged by x-ray studies, and in whom there is a quiet precordium and many of the signs we have discussed. One must realize that restrictive myocardial disease can mimic restrictive pericardial disease. In most instances the definitive resolution of this differential can be provided by cardiac

catheterization. I will briefly illustrate how cardiac catheterization can help in the differential diagnosis between constrictive pericardial disease and cardiomyopathy. In general, with constrictive disease there is a plateau of pressure: the pulmonary wedge pressure, the diastolic pressure in the pulmonary artery, the diastolic pressure in the right ventricle and the mean right atrial pressure will all be the same. In cardiomyopathy, even though the right atrial pressure may be elevated and to a degree higher than illustrated in Figure 9, the left sided pressures are much higher. This discrepancy between left and right filling pressures is a strong point favoring cardiomyopathy over constriction. There may be a rare instance in which it is impossible by all of these techniques to differentiate constrictive pericardial disease from restrictive myocardial disease, and in this situation I feel that an exploratory thoracotomy is advisable for the obvious reason that constrictive pericarditis is a potentially curable disease.

REFERENCES

1. Symposium on pericarditis. Am J Cardiol 7:1-131, Jan 1961
2. Spodick DH: Differential diagnosis of acute pericarditis. Prog Cardiovasc Dis 14:192-209, Sep 1971
3. Fowler N: Infectious pericarditis. Prog Cardiovasc Dis 16: 323-336, Nov 1973
4. Rooney JJ: Tuberculous pericarditis. Ann Intern Med 72: 73-78, Jan 1970
5. Dressler W: The post-myocardial infarction syndrome. Arch Intern Med 103:28-42, Jan 1959
6. Beaudry C: Uremic pericarditis and cardiac temponade. Ann Intern Med 64:990-995, May 1966
7. Schwartz MJ: Pericardial biopsy. Arch Intern Med 112:917-923, Dec 1963
8. Goldman MJ: RS-T segment elevation in mid- and left precordial leads as a normal variant. Am Heart J 46:817-820, Jul 1953

Prophylaxis in Meningococcus Carriers

There is a certain amount of controversy over the problem of the management of a family from which there has been a child admitted to the hospital with acute meningococcic infection in the form of meningococcemia or meningococcus meningitis. What does one do about the remainder of the family who have been exposed to the carrier responsible for the infection in the child? In the years when the meningococcus was very sensitive to sulfa drugs, the situation was an ideal one, since sulfa was very effective in treating the acute invasive infection from the meningococcus. At the same time it was extremely effective in ridding the carrier of the organism. Once resistance began to develop, however, sulfa drugs failed in both respects and the next drug used was penicillin, to which almost all strains are sensitive. Unfortunately, penicillin—though it is very effective in treating the acute severe infection with meningococcus—has very little effectiveness in clearing the carrier state. Investigators have turned to such drugs as rifampin (Rifadin®, Rimactane®) and minocycline (Minocin®) and in fact to the combination of these two antibiotics, so that these drugs do not seem to be the answer to the need to clear the carrier of the organism. My own feeling is that the best thing to do is to give no drugs to the close family contacts of a patient with meningococcemia or meningococcic meningitis, but to watch all of the persons who have been exposed to a carrier and obtain temperatures twice a day. In the event that a family member develops a fever without any explanation, it would seem indicated to treat such a child or adult exposed to meningococcus with large doses of penicillin given by mouth . . . It is quite clear that the occurrence of secondary cases within the family will be within the first week following the diagnosis of the infection in the primary case. So the worry about prevention involves primarily the first week after exposure, and it is during this week that the temperature taken twice daily could be very effective in turning up patients exposed to carriers who are coming down with an acute infection.

—SYDNEY S. GELLIS, MD, *Boston*

Extracted from *Audio-Digest Pediatrics*, Vol. 20, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pathology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Paroxysmal Cold Hemoglobinuria—1975

PAROXYSMAL COLD HEMOGLOBINURIA (PCH) is a rare disease characterized by acute intermittent massive hemolysis, frequently with hemoglobinuria, following exposure of the patient to cold. Formerly associated with syphilis, it has recently been recognized as an acute transient disorder following certain viral infections.

The diagnosis should be considered in any patient who presents with an acute hemolytic anemia and has a history of a recent viral infection, especially measles, mumps or a "flu" syndrome. Confirmation of the diagnosis depends on the demonstration of an autohemolytic bithermal antibody by the Donath-Landsteiner test: Blood is drawn from the patient and is immediately chilled. If the autoantibody against the bloodtype P antigen is present, it will attach to the patient's erythrocytes at the low temperature, followed by the early-reacting components of the complement system. On warming the blood to 37°C, the complement sequence is completed and lysis occurs. *In vivo* hemolysis occurs in the same fashion.

On admission of the patient, there may be a falling hematocrit and incipient cardiac failure. Blood selected for transfusion will usually be incompatible on crossmatch because of anti-P specificity of the antibody. Donors lacking this antigen (phenotype p) are extremely rare and it may be necessary to carry out transfusion in the patient with "least incompatible" blood, carefully prewarmed to 37°C, to save the patient's life.

Fortunately, this form of PCH is self-limited and if the patient is adequately supported during the acute hemolytic phase, the prognosis is good for complete recovery.

ROBERT E. MONCRIEFF, MD

REFERENCES

Pirofsky B: Immune haemolytic disease—The autoimmune haemolytic anaemias. Clin in Haematol 4:167-180, Feb 1975

Swisher SN: Cryopathic hemolytic syndromes, *In* Williams WJ, Beutler E, Erslev AJ, et al (Eds): Hematology. New York, McGraw-Hill Book Company, 1972, pp 498-502

Pulmonary Microembolism by Platelet Aggregates as a Cause of Unexpected Sudden Death

SUDDEN DEATH in apparently healthy young adults may be associated with extensive accumulation of aggregated platelets within small arterial vessels of the lungs. In such cases the extent of vascular occlusion is sufficient to explain death on an embolic basis. Precise figures for the incidence of this condition are not yet available, but casual observations suggest that it is not rare. The histologic identification of platelet microemboli does not require special tissue fixation or staining but does require systematic attention to blood vessel contents and familiarity with the morphology of platelet aggregation. Although the cause of rapidly fatal pulmonary platelet microembolism in man is not known, it has been induced experimentally by a prostaglandin mediated mechanism.

HUBERT PIRKLE, MD

REFERENCES

Pirkle H, Carstens P: Pulmonary platelet aggregates associated with sudden death in man. Science 185:1062-1064, Sep 20, 1974

Pirkle H, Carstens P: Massive pulmonary microembolism by platelet aggregates—A newly recognized pathologic entity associated with unexpected sudden death. Am J Path 78:10a, Jan 1975

Silver MJ, Hoch W, Kocsis JJ, et al: Arachidonic acid causes sudden death in rabbits. Science 183:1085-1087, Mar 15, 1974

T and B Lymphocytes

IT HAS BEEN appreciated for some time that there are two major compartments of the immune system. One is involved in cell mediated defenses against fungi, viruses, foreign tissues and tumors, and the other with antibody production. Although the two systems, both composed of lymphocytes, are embryologically, anatomically and functionally distinct, there is cooperation between them. They in turn cooperate with a third cellular component, the macrophage.

The mediator cells in the cellular immune system are designated T lymphocytes because of the migration of precursor cells through the thymus where they are processed or "educated." Lymphocytes committed to antibody production via transformation to plasma cells are labeled B lymphocytes. In birds the latter designation refers to the migration of precursor cells through the bursa of Fabricius. In higher mammals, since there is no known anatomical counterpart, the B refers to bone marrow origin.

T lymphocytes typically reside in the paracortical areas of lymph nodes and the periarteriolar regions of the white pulp of the spleen. B lymphocytes are found in the follicles of the lymphoid tissues. However, neither type is restricted to these areas since lymphocytes are capable of migration and are found in blood, lymph and nonlymphoid tissues.

Although T and B lymphocytes cannot be distinguished from each other by standard microscopy, it is now possible to identify them by their different surface characteristics. B lymphocytes synthesize and retain antibodies on their surfaces. These function as receptors for antigens and can be detected as "surface immunoglobulins" using fluoresceinated or radioactively labeled antisera directed against the various immunoglobulin classes. Other surface receptors include those for the F_c component of the immunoglobulin molecule and for complement (C_3). The former is detected with labeled aggregated immunoglobulin or antigen-antibody complexes and the latter by demonstrating adherence of erythrocytes (E) coated with antierythrocyte antibody (A) and complement (C), that is, rosette formation (EAC). Although monocytes (macrophages) also possess F_c and C_3 receptors and thus may absorb immunoglobulins, they do not synthesize them.

T lymphocytes are currently identified by their poorly understood capacity to adhere to sheep erythrocytes and form spontaneous rosettes (E rosettes).

New methods for identifying T and B lymphocytes are rapidly appearing. Several laboratories have prepared antisera directed against human T and B lymphocyte surface antigens, but these have yet to be widely tested for specificity. With current techniques, 15 to 30 percent of human blood lymphocytes are B lymphocytes and 50 to 70 percent are T. Variable numbers of lymphocytes do not possess any of the identifying receptors detected by these methods and have been called "null cells."

The ability to categorize lymphocytes into these major classes has already added to our understanding of immune deficiency diseases and lymphoproliferative disorders. It is apparent that many lymphomas and lymphocytic leukemias can be characterized as T or B or null and that this approach to classification has value in determining prognosis and response to therapy. However, it is also apparent that the system is far more complex than this. Within these major categories

are subpopulations of lymphocytes with different functions, antigen specificities and surface characteristics. The current thrust of much investigation is to identify and characterize these subpopulations.

JOHN W. PARKER, MD

REFERENCES

Rowlands D, Daniell R: Surface receptors in the immune response. N Engl J Med 293:26-32, Jul 3, 1975

Greaves M, Owen J, Raff M: T & B lymphocytes. New York, American Elsevier Publ Co, 1974

Hansen JA, Good RA: Malignant disease of the lymphoid system in immunological perspective. Hum Pathol 5:567-599, Sep 1974

Immune Deficiency in Adults

INITIALLY, immune deficiency was classified as either primary (congenital) or secondary. The primary form was generally considered to occur in infants and children. The secondary form, seen in adults, was due to another disease process, such as protein loss in renal or gastrointestinal disease producing hypogammaglobulinemia, or chronic lymphocytic leukemia (CLL). However, as awareness of the various deficiency states increased, some adults were found to have hypogammaglobulinemia or defects in their cellular immunity without evidence of the classically associated diseases such as CLL or Hodgkin's disease. These patients were reported to have late onset or primary acquired immunodeficiency as adults —recent literature refers to this as common variable immunodeficiency. Either arm (humoral or cellular) of the immune system may be involved, although most cases reported involve the humoral aspect. Common variable immunodeficiency is relatively common, and both men and women may be affected. A familiar pattern is not usually found. One common manifestation is recurrent infection of the sinopulmonary tract, and frequent episodes of pneumonia may lead to chronic bronchiectasis and severe respiratory insufficiency. Sinus and ear infections may lead to diminished hearing. Another manifestation is a sprue-like syndrome with a wide range of malabsorption difficulties, and gastrointestinal tissues in some cases show nodular lymphoid hyperplasia. Tissues of various organs may show noncaseating granulomas, and there may be generalized hyperplasia of the reticuloendothelial system. A patient's serum may contain a wide variety of autoantibodies.

Diagnosis is usually made by quantitation of serum immunoglobulins and evaluation of cellular immunity—that is lymphocyte count and skin tests. Determination of the number of B-cells in peripheral blood—a more sophisticated test—was not always helped in the evaluation of hypogammaglobulinemia, as the number of cells varies from 0 to "normal." In some cases where the B-cell number has been "normal," there is evidence of a suppressor effect by T-cells. Therefore it appears that all variations of production and secretion may be found, so care should be taken in making the diagnosis and assessing individual cases.

STEBBINS B. CHANDOR, MD

REFERENCES

Rosen F: Primary immunodeficiencies. Pediatr Clin North Am 21:533, Aug 1974

Waldman TA, Durm M, Broder S, et al: Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinemia. Lancet 11:609, Sep 14, 1974

Amniotic Fluid Protein of the Second Trimester

SECOND TRIMESTER transabdominal amniocentesis and subsequent laboratory examination of the constituents of the amniotic fluid is of established value in the identification of fetal morbidity.

Amniotic cell cultures with specific enzyme assays is of diagnostic value in over 20 inborn defects. High levels of amniotic fluid alpha-fetoprotein (AFP) are now considered a good marker of neural tube defects such as anencephaly and spinal bifida. This observation of elevated AFP is most valid and of pragmatic value between 14 and 18 weeks gestation when diagnosis of a major developmental neural abnormality is to be followed by abortion. Additional amniotic proteins, especially the immunoglobulins, have not yet been completely evaluated. However, some measurements are known. It is possible to identify and quantitate albumin, immunoglobulin G (IgG), transferrin and alpha-1 antitrypsin in "normal" midtrimester amniotic fluid specimens with the use of commercially available single radial immunodiffusion plates and monospecific antisera.

Second trimester amniotic fluid also contains immunoglobulin A (IgA), Gc globulin and alpha fetoglobulin. Immunoglobulin M (IgM) and alpha-2-macroglobulins are not detected in normal fluids with commercially available reagents. IgG does cross the placenta but the other immunoglobulins apparently do not. Therefore, the

presence of immunoglobulins probably reflects fetal production and an increase could herald infection of the fetus. Elevated concentrations of IgG may relate to disease of the fetus or mother. However, IgG does not appear sufficiently increased for diagnostic use during the 1st and 2nd trimesters in rubella intrauterine infections. Fluid "drifts" from the fetal lung to the amniotic cavity carrying with it suspended exudative or transudative material. Therefore, alterations of IgA (secretory type) could indicate current or past immunologic challenge of the developing respiratory tree. Further study of the amniotic fluid proteins, particularly the immunoglobulins, appears warranted.

GERRIT D'ABLAING III, MD

REFERENCES

Nadler HL: Prenatal diagnosis of inborn defects—A status report. Hospital Practice 10:41-51, Jun 1975

Brock DJ, Nelson MM: Amniotic fluid proteins in pregnancy complicated by anencephaly. J Obstet Gynecol Commonw 81: 177-181, Mar 1974

Goldsmith C, d'Ablaing G, Chandor S: Amniotic-fluid proteins. Lancet 1:367-368, Mar 1974

Acute Viral Hepatitis

EPIDEMIOLOGIC AND SEROLOGIC data have begun to make a convincing case for the existence of more than two hepatitis viruses. The most thoroughly studied is hepatitis B virus (HBV), the agent for the long incubation disease (45 to 180 days). HBV is most readily transmitted percutaneously. In an infected person it may be present in most body fluids and secretions but it cannot usually be identified in specimens of stool. HBV produces the disease most closely corresponding to the older term "serum hepatitis." The virus has a complex life cycle. The 20 nanometer (nm) dioxyribonucleic acid *core* of HBV is replicated in nuclei of infected hepatocytes, and is immunologically characterized as hepatitis B core antigen (HBcAg).

An antigenically distant lipoprotein outer surface of HBV is produced in the endoplasmic reticulum of infected hepatocytes. The surface antigens are called hepatitis B surface antigen (HBsAg). A unique characteristic of HBV is the excessive production of theoretically noninfective HBsAg in 20 nm particles and filaments, far in excess of the amount of viral core. HBsAg production is sufficient for the particles to be demonstrable in serum as precipitable antigen, forming the basis for the currently used agglutination, counterelectrophoresis and radioimmunoassay diagnostic techniques. HBsAg particles have a group specific antigen, a. In addition, several allelic subtypes (such as d and y, w and r) have been identified. Another mysterious antigen, separate and distinct from HBsAg particles, is found in sera of some patients with acute viral hepatitis type B (VH-B) and in sera of most patients with chronic varieties of VH-B. This is the e antigen; perhaps e is related to infectivity.

In patients recovering from HBV, anti-HBc develops, and weeks later anti-HBs develops in some. In all patients who recover completely there is a tissue immune response to HBsAg, as well as apparent lifelong immunity to VH-B. In 10 to 15 percent of patients with icteric Ac VH-B, some chronic manifestation of disease occurs. In 7 to 12 percent, the asymptomatic, benign, persistent viral hepatitis type B (PVH-B) develops and in 3 percent or fewer the progressive chronic active viral hepatitis type B (CAVH-B) occurs. Within the past year, development of heat-treated HBsAg offers considerable promise as a vaccine.

Hepatitis A virus (HAV)—the 15 to 45 day incubation, fecal-oral agent that produces acute viral hepatitis type A (Ac VH-A, formerly called infectious or epidemic hepatitis)—has recently been seen in stool specimens of patients who were in the prodrome or the very early stages of the disease. The particles are identified by immunoelectron microscopy, in which particles isolated from stool specimens of patients suspected of having VH-A acquire a fuzzy antibody coated surface and agglutinate when convalescent serum of prior VH-A patients is added. In patients who acquire Ac VH-A, anti-HAV develops during the height of clinical illness and they then have lifelong immunity. Only lack of a method of obtaining sufficient HAV virus particles prevents routine testing for anti-HAV as a diagnostic procedure. There is no evidence that VH-A ever progresses to chronic liver disease, and it rarely produces fulminant fatal disease.

Studies of the immune response and the incubation periods in patients with posttransfusion hepatitis show that in most patients who acquire a non-B type of acute hepatitis, a disease that has an incubation period intermediate between that of Ac VH-A or Ac VH-B develops. In such patients, disease or convalescence is not associated with antibody or tissue immune response to either HAV or HBV. Neither particles nor candidate virus have been recognized in body products or fluids.

Animal inoculation that has been successful (although not economically feasible for diagnosis) for HV-A and HV-B is still under investigation for viral hepatitis non-A non-B (VH-NAB). Apparently the incidence of development of chronic disease after acute VH-NAB is similar to that after Ac VH-B.

Recent advances and knowledge regarding viral hepatitis were reviewed at the National Academy of Sciences in Washington, D.C., in March 1975. The entire proceedings of that meeting have been published in the *American Journal of Medical Science,* Vol 270, July-August 1975.

ROBERT L. PETERS, MD

Estrogen Receptor Protein Assays in Human Breast Cancer

THE IMPORTANCE of estrogen receptor (ER) protein assays in the evaluation of endocrine therapy for metastatic breast cancer is well established. In general, if there is a negative tumor ER value, a patient's response to endocrine therapy with tumor regression is very poor. If the breast tumor ER value is positive, a significant response to endocrine therapy including ablative surgical operation is seen in 55 to 60 percent of patients.

In a recent review by McGuire, he has summarized strong but not necessarily conclusive evidence to support several points:

- Tumors from postmenopausal patients contain higher ER values than premenopausal patients. Endogenous estrogen occupying receptor sites in premenopausal patients may cause low absolute ER values.
- ER values from primary or metastatic breast tumor are of equal value in predicting response to endocrine therapy.
- No significant correlation was seen between the presence of ER in tumor and (1) positive or negative axillary lymph nodes, (2) location of tumor, and (3) histologic type of tumor.
- A negative correlation was seen between the presence of ER and the size of the primary tumor. The larger tumor may contain more necrotic tissue and less ER.
- No correlation was seen between absolute ER values and percentage of patients responding to endocrine therapy or duration of remission.

Many described assay methods for ER in breast tumors are complex methods which involve large numbers of tubes and are difficult to adapt as routine assays in a hospital clinical laboratory. Recently we described a method adapted from McGuire and de la Garza and Leung and coworkers which provides a feasible approach to the assay of estrogen tissue receptors. The method yields quantitative results reportable in femto moles (10^{-15} ml) of estradiol bound per mg of protein, a dissociation constant (Kd) from a Scatchard plot and a binding index—all in a protocol that allows several patient samples and target and nontarget controls to be assayed in one run.

ROBERT M. NAKAMURA, MD

REFERENCES

McGuire WL: Endocrine therapy of breast cancer. Ann Rev Med 26:353-363, 1975

Johnson RB, Nakamura RM, Libby R: Simplified Scatchard plot assay for estrogen receptor in human breast tumor. Clinical Chem 1975 (In Press)

Leung B, Manaugh LC, Wood DC: Estradiol receptors in benign and malignant tumors of the breast. Clin Chim Acta 46: 69-76, Jun 14, 1973

Gallium-67 Scintigraphy and Subphrenic Abscesses

SUBPHRENIC ABSCESSES present one of the more challenging of clinical problems. An insidious onset and obscure presence frequently render diagnosis difficult and often delayed. Conventional liver-lung scintigraphy, when correlated with roentgenographic findings, has offered some assistance in the diagnosis of subphrenic abscess. However, complicating clinical features frequently cause misleading or equivocal results.

Gallium-67 (^{67}Ga) scintigraphy is a new approach to the diagnosis of subphrenic abscess, and one that is preferable to other scintigraphic approaches. The criteria associated with right subphrenic abscess using ^{99m}Tc labeled radiopharmaceuticals and conventional liver-lung imaging technique (that is, separation and displacement of hepatic and pulmonary images on appropriate views) are nonspecific and may be seen in a variety of conditions. Basilar atelectasis, pleural or peritoneal effusions, pulmonary emboli, emphysema, cirrhosis or cysts may all yield similar findings. The use of ^{67}Ga can increase the specificity of diagnosis by eliminating these noninflammatory causes of false positive liver-lung studies. Gallium-67 is even more valuable in a left subphrenic abscess because conventional liver-lung scintigraphy in this area is difficult and unreliable due to the position of the heart and vari-

ability in size and position of the left hepatic lobe and spleen.

Suggested mechanisms of ^{67}Ga localization in inflammatory sites include ^{67}Ga protein complexes collecting about the inflammatory site and the *in vivo* labeling of granulocytic leukocytes that migrate to the inflammatory focus. A decrease in circulating granulocytes has correlated with both a diminution in intensity and a delay in onset of ^{67}Ga detection in experimental inflammation.

G. Bruce Hopkins, MD

REFERENCES

Gelrud LG, Arseneau JC, Milder MS, et al: The kinetics of ^{67}Gallium incorporation into inflammatory lesions—Experimental and clinical studies. J Lab Clin Med 83:489-495, Mar 1974

Hopkins GB, Mende CW: Gallium-67 and subphrenic abscesses—Is delayed scintigraphy necessary? J Nucl Med 16:609-611, Jul 1975

Cystic Medionecrosis and Dissecting Aneurysm

Cystic medionecrosis has been generally accepted as the cause of dissecting aortic aneurysm following its meticulous description by Erdheim more than 40 years ago. Surprisingly, he encountered the lesion not in dissecting aneurysm, but in two cases of rupture of nonsyphilitic aneurysm of the ascending aorta.

Briefly, the lesion is characterized by accumulations of mucoid substance that gradually coalesce to form cysts that interrupt the continuity of the elastica and sometimes muscle and collagen as well. Use of the term "cystic" seems objectionable because the cysts lack a distinct lining, while the term "medionecrosis" is inappropriate since necrosis is seldom demonstrable. Recent reports suggest that cystic medionecrosis is not the most frequently encountered lesion in dissecting aneurysm, but is a consistent finding only in dissections (aneurysms) that complicate the infrequent Marfan's syndrome, and in the rare instances of aneurysm of the ascending aorta that occur in the absence of syphilis.

Cystic medionecrosis occurs principally with lesions of elastic tissue rather than muscle in the aorta. Muscle lesions are considerably more frequent than elastic lesions in dissecting aneurysm and also correlate better with such clinically associated factors as hypertension and increasing age.

It seems that the term "cystic medionecrosis" has outlived its usefulness and should be discarded in favor of a designation which specifies the defective components of the vessel wall, which may include muscle, elastic tissue, collagen or ground substance.

Albert E. Hirst, MD

REFERENCES

Gore I, Hirst AE Jr: Dissecting aneurysm of the aorta. Prog Cardiocasc Dis 16:103-111, Sep-Oct 1973

Layman TE, Wang Y: Idiopathic cystic medionecrosis and aneurysmal dilation of the ascending aorta. Med Clin N Amer 52:1145-1156, Sep 1968

Gore I, Seiwert VJ: Dissecting aneurysm of the aorta: Pathologic aspects—An analysis of eighty-five fatal cases. Arch Pathol 53:121-141, Feb 1952

BCG Infections in Cancer Patients

Bacille Calmette Guérin (BCG) vaccine is being administered to some cancer patients as one element of therapy. The vaccine is a living culture of Mycobacterium bovis that has been attenuated in virulence, but the degree of attenuation has not been completely standardized throughout the world. In immunized people who are otherwise healthy, localized infections develop that sometimes progress to lymphadenitis, occasionally with suppuration of the nodes as described by Wilson. Disseminated BCG disease is even more likely to develop in patients with cancer, as reported by Aungst and co-workers.

BCG vaccine grows easily in culture, and it can be grown from infected nodes and other tissues by the same methods that are used for growing Mycobacterium tuberculosis. In culture, it has the biochemical reactions of Mycobacterium bovis, but can be further identified as the BCG strain by its inability to produce progressive disease in guinea pigs, and by resistance to lysis by mycobacteriophage 33-D.

Pasteurization of milk and control of bovine tuberculosis have almost eradicated M. bovis as a cause of human disease in the United States, and recovery of M. bovis from a patient who has received BCG vaccine strongly suggests that the organism is the vaccine strain. Both BCG and M. bovis are almost always susceptible to isonicotinic acid hydrazide (Isoniazid®), rifampin, ethambutol, streptomycin and para-aminosalicylic acid. Therefore, mycobacterial therapy can be started before the culture has been definitively identified as BCG.

William P. Lewis, PhD

REFERENCES

Aungst CW, Sokal JE, Jager BV: Complications of BCG vaccination. Proc Am Assn Cancer Res 14:108, Mar 1973

Jones WD Jr: Differentiation of known strains of BCG from isolates of Mycobacterium bovis and Mycobacterium tuberculosis by using mycobacteriophage 33 D. J Clin Microbiol 1:391-392, Apr 1975

Wilson GS: The hazards of immunization. London, Athlone Press, 1967, pp 239-249

Alpha$_1$-Fetoprotein

ALPHA$_1$-FETOPROTEIN (AFP) is a serum protein found in low concentrations in normal adults (<10 nanogram (ng) per ml); concentrations well above this are found in fetal serum and maternal sera (up to 400 ng per ml) and in certain pathological conditions. AFP is synthesized normally by fetal liver, yolk sac and gastrointestinal tract. In adults, serum concentrations above normal may be found associated with tumors arising from or containing elements of these tissues—that is, hepatoma, teratomas (endodermal sinus tumors) and rarely gastrointestinal tumors—as well as with conditions in which liver cell damage or regeneration or both occur (hepatitis, cirrhosis). Determination of the exact serum concentration of AFP during the course of the above diseases may be useful in diagnosis and management.

- *Hepatoma.* In our experience in San Diego, the sera of 22 out of 25 patients with hepatoma had AFP concentrations greater than 350 ng per ml. With growth of a tumor that produces AFP the serum concentration will rise steadily. Following successful surgical removal the serum AFP concentration will fall to normal levels. With recurrence or metastasis, the serum AFP concentration will again rise. Successful chemotherapy may result in a stabilization or decline in sera AFP concentration.
- *Ovarian and testicular tumors.* Teratomas containing endodermal sinus tissue (yolk sac) or fetal liver components will also produce notably elevated serum AFP concentrations (up to 1,000 ng per ml). Therefore, serum AFP can be used for diagnosis and follow-up of these tumors in a way similar to that for hepatomas.
- *Other tumors.* AFP elevations are rarely found with primary gastrointestinal tumors. Elevations above the normal upper limit of 40 ng per ml are found in a small percentage of patients with stomach, pancreas or biliary tract tumors. Elevated AFP is rarely found with other primary tumors, such as lung tumors, and usually only when metastases to the liver have occurred. The AFP concentrations in these circumstances are usually less than 350 ng per ml.
- *Cirrhosis.* Elevations up to 1,000 ng per ml are occasionally found. Serial samples should be obtained since increasing concentrations to above 350 ng per ml suggest development of hepatoma.
- *Viral Hepatitis.* Transient elevations above 350 ng per ml are common. In cases of fulminant hepatitis the serum concentration of AFP may reflect hepatic regeneration. A return to normal is associated with clinical recovery.
- *Pregnancy.* Concentrations up to 400 ng per ml are found in maternal serum during normal pregnancy with the peak levels occurring during the 28th to 36th weeks of pregnancy. Higher concentrations may indicate fetal death, multiple pregnancy or birth defects. Amniotic fluid concentrations of AFP at 15 to 20 weeks gestation range between 15 to 500 ng per ml, but may become notably elevated (>1,000 ng per ml) in association with open neural tube defects and less so with other congenital anomalies which can cause leakage of fetal proteins into amniotic fluid.

AFP determinations may be ordered from: Chemistry Department (c/o Pam McNeil), University Hospital, San Diego, CA 92037.

Samples of at least 1 ml of frozen or azide-preserved serum should be forwarded. Results can be expected within one to two weeks.

S. SELL, MD
H. T. WEPSIC, MD

REFERENCES

Ruoslathi E, Pihko H, Seppala M: Alpha-fetoprotein: Immunochemical purification and chemical properties—Expression in normal state and in malignant and non-malignant liver disease. Transplant Rev 20:38-60, 1974

Sell S, Wepsic HT: Alpha-fetoprotein, *In* FF Becker (Ed): The Liver. New York, Marcel Dekker, Inc, 1975, pp 773-820

Current Status of Anaerobic Bacteriology and Anaerobic Infections

SIMPLIFIED PROCEDURES permit all laboratories to do reliable anaerobic bacteriology. Anaerobic jars, including the convenient GasPak®, are effective for clinical work. Conventional or simple tests provide satisfactory identification of five anaerobic groups accounting for 75 percent of infections—Bacteroides fragilis, Bacteroides melaninogenicus, Fusobacterium nucleatum, anaerobic cocci and Clostridium perfringens. Good guides to susceptibility testing are available.

Clinicians must avoid normal flora in collecting specimens. Transtracheal aspiration permits documentation of pulmonary infection. Specimens must be transported anaerobically.

The incidence of anaerobes in infection is impressive. Ninety percent of brain and lung abscesses contain anaerobes, with no aerobes in two thirds of the cultures. Over 90 percent of cultures

in aspiration pneumonia yield anaerobes—of which half to two thirds are purely anaerobic. In thoracic empyema (non-postoperative), 75 percent of specimens yield anaerobes—half are the exclusive isolates. Intraabdominal infections contain anaerobes 90 percent of the time, with only 10 percent pure. Anaerobes are found in 70 percent of female genital tract infections, 30 percent in pure culture. Other common anaerobic infections include chronic otitis, mastoiditis and sinusitis; oral and dental infections; bacteremia; liver abscess, and soft tissue infections.

Surgical therapy (drainage, debridement) is essential. Useful antimicrobial drugs include penicillin G or ampicillin (except for B. fragilis), carbenicillin, chloramphenicol and clindamycin. Doxycycline and minocycline are less effective and require susceptibility tests. Metronidazole, still experimental, looks promising.

SYDNEY M. FINEGOLD, MD

REFERENCES

Gorbach SL, Bartlett JG: Anaerobic infections. N Engl J Med 290:1177-1184, 1237-1245, 1289-1294, May 1974

Sutter VL, Vargo VL, Finegold SM: Wadsworth Anaerobic Bacteriology Manual. Los Angeles, Univ. of California, Los Angeles Extension Division, 2nd Edition, 1975, p 106

ADVISORY PANEL TO THE SECTION ON PATHOLOGY

STEBBINS CHANDOR, MD, *Chairman, Los Angeles*
CMA Scientific Board
Chairman, CMA Section on Pathology

JOSEPH H. MASTERS, MD
CMA Section on Pathology
Secretary
Fair Oaks

EMMETT REILLY, MD
CMA Section on Pathology
Assistant Secretary
Inglewood

ROBERT S. COX, JR., MD
San Jose

W. JANN BROWN, MD
University of California, Los Angeles

FRANK DUTRA, MD
CMA Scientific Board
Castro Valley

BRIAN S. BULL, MD
Loma Linda University

DAVID KORN, MD
Stanford University

SEFTON R. WELLINGS, MD
University of California, Davis

EDWARD R. ARQUILLA, MD
University of California, Irvine

COLIN M. BLOOR, MD
University of California, San Diego

GEORGE BRECHER, MD
University of California, San Francisco

STEBBINS B. CHANDOR, MD
University of Southern California
Los Angeles

JOHN H. MANWARING, MD
San Rafael

PHILLIPS GAUSEWITZ, MD
La Jolla

EDITORIALS

Forward Plan for Health — For the Years 1977-1981

THE UNITED STATES PUBLIC HEALTH SERVICE (USPHS) has again come to the forefront within the federal government by developing an updated Forward Plan for Health which the Service would like to see implemented in the years 1977-1981. The document is a thoughtful one and should be studied by physicians and anyone else interested in the future of health care in this nation. It is written in "governmentese" and no doubt primarily for government consumption, but from it one can glean what the USPHS at least, would like to do and see done.

The plan is divided into several "themes" but one of particular interest is entitled "Assuring the Quality of Health Care." This, the plan says, attempts to provide a framework within which diverse federal health responsibilities may be integrated into a coherent program to maintain and improve the quality of health services in the United States. To accomplish this, knowledge is to be developed and disseminated regarding the efficacy, safety and cost of "medical procedures" and methods of assessing and improving the quality of "health care interventions." "Organizational and administrative entities" are to be established to improve the quality of performance "through a variety of mechanisms." The plan seems to suggest that while the Professional Standards Review Organizations (PSRO's) and the private sector will develop the norms, criteria and standards of care, these will be "validated" as to efficacy, safety and cost by the federal government. It states further that "even if important aspects of clinical medicine are validated, and acceptable criteria and standards are developed, it will not be possible to assure quality without an administrative structure to see to it that practice is aligned to theory."

One should not fault the USPHS for developing a plan for health. Costs are rising and funds, whether personal, government or third party insurance carrier, are limited. Some kind of projection or plan is needed to assure reasonable quality of health care at reasonable cost, and no one else has come up with anything. But it is suggested that the plan may be faulted for its approach which seems not to have included any solid input from the real world of medical practice and health care, that is from the professionals and others who will be expected to make the plan work. It appears to be a plan of the government by the government for the government, when what is really needed is a plan of the people by the people for the people—the people in this instance being those who provide, receive and ultimately pay for health care services. Leaving aside for the moment any philosophical questions such as whether the government is really the people or whether the people should serve the government or the government should serve the people, the real question is whether there can ever be successful planning for any complex, terribly interdependent and very human social and economic system such as health care is in this nation without substantial input and participation from a broad spectrum of those who work within that system. There is some experience in the last decade that suggests a positive correlation between input from the private sector in planning and the ultimate workability and success of a program. For example, there was considerable input into Title XVIII (Medicare)—which has worked reasonably well—and little or none into Title XIX (Medicaid)—which has not. There may be an important message here.

There can be no doubt that the cost bind in health care and the need to be sure of quality while attempting to contain costs are immediate and pressing problems shared by both the public and private sector of our society. The federal government and the USPHS may be commended for leadership in developing a Forward Plan for Health—1977-1981. But the thrust of the theme "Assuring the Quality of Health Care" points clearly to a determination to impose the will of the federal government upon health care services and the health care system. This is proposed to be done concurrently with the development of the necessary knowledge and methods to assure quality which the plan admits are not yet adequately known. One wonders if this does not portend more restraints, inefficiency and friction within the system—with their attendant higher costs with little or no predictable benefit con-

sidering the admitted present state of our knowledge of quality assurance.

It is suggested that the Forward Plan for Health —1977-1981 will have served a most useful purpose if it becomes a stimulus to the private sector health care industry, which is one of the largest and most complex in the United States, to find effective ways to plan *with government* for the future of health care in this nation. This will require (1) that the autonomous and independent organizations, institutions and associations in the private sector find ways to get together for effective short- and long-range planning and (2) that the federal government will be willing to work together with the private sector more as the servant rather than as the master of the people. Whether this can or will be done remains to be seen. The issue is a fundamental one for the survival of the rule of the people by the people in an increasingly complex and interdependent democratic society.

Perhaps there should be some sort of ad hoc coalition of some of the principal organizations and agencies in the private sector to identify health care goals and to see if a coordinated planning effort in the private sector is possible. If this could be done in the Bicentennial year and then coordinated with government planning, health care in this nation could enter a new era in which whatever restrictions and controls there might be would be developed with the system rather than imposed upon it. It is only human nature to work much harder to make one's own plans succeed than someone else's.

—MSMW

Hemolytic Uremic Syndrome

THE HEMOLYTIC UREMIC SYNDROME (HUS) is a clinical entity composed of uremia, hemolytic anemia with characteristically fragmented cells, and usually thrombocytopenia. This syndrome was brought to medical attention in 1955 by Gasser and co-workers.[1] Since then, many cases have been reported with the result that a much broader concept of the syndrome has evolved. In the Specialty Conference appearing in this issue of the JOURNAL, Mendoza uses the case history of a child with HUS primarily to examine in detail the problem of acute renal failure, the prominent clinical challenge in this syndrome. Indeed, it is important that HUS be repeatedly discussed—particularly in California where its occurrence is considered endemic. Since 1963 our group has seen an average of six new cases each year. Because prognosis appears to be influenced by prompt diagnosis and management, physicians in the western United States should know its characteristics.

The HUS has worldwide distribution, particularly in areas with temperate climates. California, Argentina, South Africa and the Netherlands are considered endemic areas. Most cases occur sporadically, although scattered clusters have been reported. Seasonal variation appears to occur in the San Francisco bay area, with the highest incidence in September. There is no sex predilection. The average age of onset is 2 to 5 years. An exception is Argentina where the average age is much younger—13 months; however, even there children as old as 9 years[2] or older[3] have been reported. The syndrome is now being recognized in women, particularly postpartum[4] or after the use of contraceptive pills.[5]

Characteristically, there is a virus-like prodrome, with prominent gastrointestinal symptoms (such as diarrhea, which frequently becomes bloody, and severe abdominal pain). Upper respiratory symptoms may precede these findings. Abdominal pain is recognized more frequently in older children and often leads to misdiagnoses (for example, ulcerative colitis, intussusception and acute appendicitis). On initial examination, the patient is usually pale and edematous; hypertension and hepatomegaly are common. Hemoglobin is low, and levels of blood urea nitrogen are elevated in almost all patients. Leukocytosis, reticulocyte counts greater than 5 percent, and blood and protein in the urine are frequent findings. Thrombocytopenia is present in most cases, the levels of coagulation Factors V, VIII and X are usually not decreased; fibrin split products are more often absent than present. Usually prothrombin time and partial thromboplastin time are prolonged.

As noted by Mendoza, there is no single recognized etiologic agent; rather, several dif-

ferent viruses have been implicated, as well as some bacteria. Epidemiologic studies have shown multiple rising viral titers in family members and other close contacts in whom HUS does not develop. It is unknown why the clinical syndrome develops in some people and not in others. Disappointingly few organisms have been identified, despite extensive investigations.

Although Mendoza presents a different impression, most authorities agree that the pathophysiology of HUS results from accelerated intravascular coagulation. The histologic renal lesions are distinct and characteristic.[6-8] The degree of involvement may vary from minimal thickening of the glomerular capillary wall with prominent mesangeal areas to bilateral cortical necrosis. By light microscopy, the observed abnormalities are quite consistent with lesions of accelerated intravascular coagulation. Electron microscopic findings are unequivocal; electron dense, fibrillar material is observed within the widened radiolucent subendothelial area and between the cytoplasm of endothelial and mesangeal cells. Thrombi, with periodicity characteristic of fibrin, are seen frequently in the capillary lumina. Numerous intact or disintegrating platelets line the glomerular capillary walls. Immunofluoroscopy confirms the deposition of fibrin in the glomerular tufts in tissue examined within the first four to six weeks after onset of the disease. Only rarely has deposition of immunoglobulins been documented. Intravascular thrombosis, *not* restricted to the kidney, is reported in many children dying after prolonged severe azotemia. The histologic lesions are similar to those seen in the generalized Shwartzman phenomenon, and are much more consistent with accelerated intravascular coagulation than are the blood studies.

Mendoza's patient recovered completely, although dialysis was delayed until azotemia was more severe. Our experience at the University of California, San Francisco, indicates that immediate peritoneal dialysis is preferable to delay, and favorably influences the outcome. This position is supported strongly by the findings of Kaplan and co-workers.[9] Dialysis relieves overhydration, restores normal blood pressure (or makes hypertension more easily controlled), averts impending heart failure and permits red blood cell transfusion with less hazard of overloading the circulation. Azotemia and hyperkalemia are alleviated and although the use of digitalis and diuretics may be avoided, administration of aluminum hydroxide and sodium polystyrene sulfonate (Kayexalate®) are usually required for control of elevated serum phosphate and potassium levels. Perhaps permanent damage to the anterior walls can be avoided, if hypertension is prevented early or controlled. As Mendoza points out, 20 to 25 percent of caloric needs are required to minimize catabolism. Concentrated glucose solutions are less sclerosing in larger veins and better nutrition can be maintained if a catheter is placed in the vena cava. Adequate nutrition is important not only to minimize developing azotemia but also to reduce susceptibility to infection.

In all published experience, better symptomatic management has improved the prognosis in HUS. However, mortality or permanent renal insufficiency remain high (between 10 and 20 percent). The findings associated with a poor prognosis are prolonged duration of anuria and initial convulsions. However, there is no initial way to predict duration of anuria nor is it possible to establish the mechanism responsible for the seizure—such as uremia, edema, hyponatremia and thrombosis. Since increased intravascular coagulation is a recognized integral part of this disease and thrombosis is associated with renal necrosis, it is reasonable to use anticoagulant agents as quickly as possible in order to interfere with the process or dissolve the thrombi already present or both. In our series of 73 patients with HUS, 8 of 13 who were anuric for more than six days recovered completely following the use of heparin given intravenously. Only one of seven recovered from a similar duration of anuria treated symptomatically only. Similar experience has been reported by some,[10] while no benefit with administration of heparin has been reported by others.[9] Quite recently there have been a number of reports of favorable outcome following the use of streptokinase,[11] or aspirin or dipyridamole—or both of these.[12]

Since HUS is a common cause of childhood renal failure, a well organized collaboration study is in order, not only to understand the syndrome in more depth but to develop specific therapy.

CAROLYN F. PIEL, MD
Associate Professor of Pediatrics
University of California, San Francisco

REFERENCES

1. Gasser C, Gautier E, Steck A, et al: Hamolytisch-uramische Syndrome: bilaterale Nierenrindennekrosen Bei Akuten Erworbenen Hamolytischen Anamien, Schweiz med Wschnshr 85:905, 1955
2. Gianantonio CA, Vitacco M, Mendihaharzu F, et al: The Hemolytic-Uremic syndrome. Nephron 11:174-192, 1973
3. Ramirez J: Personal communication. 1975
4. Clarkson AR, Lawrence JR, Meadows R, et al: The haemolytic uraemic syndrome in adults. Quart J Med 39:227-244, 1970
5. Brown CB, Clarkson AR, Robson JS, et al: Haemolytic

uraemic syndrome in women taking oral contraceptives. Lancet 1:1479-1481, 1973
6. Piel CF, Goodman R, Beck J: Ultramicroscopic glomerular lesions in hemolytic uremia. Clin Res 18:225-226, 1970
7. Habib R, Courtecuisse V, Leclerc F, et al: Etude anatomopathologique de 35 observations de syndrome hemolytique et uremique de l'enfant. Arch Franc Ped 26:391-416, 1969
8. Vitsky BH, Suzuki Y, Strauss L, et al: The hemolytic uremic syndrome, a study of renal pathologic alterations, Am J Path 57:627-648, 1969
9. Kaplan BS, Katz J, Krawitz S, et al: An analysis of the results of therapy in 67 cases of the hemolytic-uremic syndrome. J Pediat 78:420-425, 1971
10. Lieberman E: Hemolytic-uremic syndrome. J Pediat 80:1-16, 1972
11. Powell HR, Ekert H: Streptokinase and anti-thrombotic therapy in the hemolytic-uremic syndrome. J Pediat 84:345-349, 1974
12. Arenson EB, August CS: Preliminary report: Treatment of the hemolytic-uremic syndrome with aspirin and dipyridamole. J Pediat 86:957-961, 1975

Calcium Metabolism

IN THEIR REVIEW, elsewhere in this issue, on calcium and skeletal metabolism, Deftos and his colleagues touch upon many practical issues of interest to clinicians. Of the three hormones concerned with mammalian calcium homeostasis, parathyroid hormone (PTH) and vitamin D may prove to be the two most important. Soon after the independent and nearly simultaneous discovery of calcitonin by Copp[1] and Munson,[2] doubt arose as to whether this hormone plays an important physiological role in adult mammals. Some investigators viewed calcitonin as a vestigial hormone, interesting to investigators but not to clinicians. As highlighted in the review, all of this is changing. Evidence for a physiological role of calcitonin is becoming increasingly convincing, and the importance of calcitonin in diagnosis as well as treatment is now firmly established.

While recent advances in the understanding of vitamin D and calcitonin represent dramatic new insights, abnormal parathyroid function continues to dominate clinicians' thinking. Radioimmunoassays of PTH are at last available and provide an important new diagnostic tool. Properly carried out and interpreted, these assays can provide highly useful information. Poorly carried out or misinterpreted, they lead to confusion. Unfortunately, some commercial laboratories fail to provide clinicians with adequate information concerning the affinity characteristics of the antiserum used. No two antisera are exactly alike. Some possess binding sites predominantly for the intact, 84 amino acid peptide, some predominantly for fragments and some for all immunoreactive forms of circulating PTH. Since the native hormone and fragments possess widely differing biological and kinetic properties, interpretation of assay results depends on what is being measured. The predominant current evidence favors the view that PTH fragments are generated by peripheral metabolism of the native hormone. Metabolism is accomplished by several organs, notably kidney and liver.[3] The biological meaning of metabolism is under study in several laboratories, but at present no conclusive information exists. Metabolism may represent merely catabolic disposal of secreted hormone. Alternatively, it may represent activation.

Increasing application of the radioimmunoassay of PTH in the study of human disease has made it evident that circulating PTH is increased under many circumstances. Nonionic stimulation of PTH secretion has received attention only recently, but enough information is available to suggest that this will prove to be very important. In this regard, Fischer's demonstration that catecholamines stimulate PTH secretion is of particular interest.[4] When a field advances rapidly and questions emerge more rapidly than answers, clinicians would be well-advised to adopt a conservative attitude. Treatment should not be undertaken because of assay results alone, but only when these results seem to be consistent with findings from more traditional assessments of a patient's problems.

This caveat is pertinent particularly to asymptomatic and normocalcemic hyperparathyroidism as discussed in the review. I am ambivalent about the authors' statement that, in an asymptomatic patient, " . . . it is probably prudent to operate in most patients, unless there is contraindication to surgical operation." An asymptomatic patient is likely to have a mild form of hypercalcemic (primary) hyperparathyroidism and is the one in whom finding the abnormal parathyroid gland(s) is difficult. Even expert parathyroid surgeons may find this a vexing problem. Under any circumstances, the need for the services of an expert parathyroid surgeon cannot be overemphasized. It is tragic that surgeons with only a casual acquaintance with the problems of parathyroid surgical procedures continue to embark on this form of operation.

The review does not mention the controversial issue of the indications for preoperative localization of abnormally functioning parathyroid glands.[5,6] There is general agreement that this is indicated in a patient with symptomatic hyperparathyroidism in whom parathyroid surgical operation has previously been unsuccessful. One could make a good argument for preoperative

localization studies in patients with minimal hyperparathyroidism for whom surgical correction of the disease is recommended. These studies should facilitate the task of the surgeon. Whether such studies are indicated in patients with uncomplicated well-established disease is doubtful. In such patients, a highly experienced parathyroid surgeon is likely to carry out a curative procedure in 90 percent or more of cases. Under this circumstance, the cost:benefit ratio may not justify preoperative localization studies.

ERIC REISS, MD
University of Miami School of Medicine
Miami, Florida

REFERENCES

1. Copp DH, Cameron EC, Cheney BA, et al: Evidence for calcitonin—A new hormone for the parathyroid that lowers blood calcium. Endocrinology 70:638-649, 1962
2. Hirsch PF, Gauthier G, Munson PL: Thyroid hypocalcemia principle and recurrent laryngeal nerve injury as factors affecting the response to parathyroidectomy in rats. Endocrinology 73:244-252, 1963
3. Canterbury JM, Bricker LA, Levey GS, et al: Metabolism of bovine parathyroid hormone—Immunological and biological characteristics of fragments generated by liver perfusion. J Clin Invest 55:1245-1253, 1975
4. Fischer JA, Blum JW, Binswanger U: Acute parathyroid hormone response to epinephrine *in vivo*. J Clin Invest 52:2434-2440, 1973
5. Reiss E, Canterbury JM: Primary hyperparathyroidism: Application of radioimmunoassay to differentiation of adenoma and hyperplasia and to preoperative localization of hyperfunctioning parathyroid glands. N Engl J Med 280:1381-1385, 1969
6. Powell D, Shimkin PM, Doppman JL, et al: Primary hyperparathyroidism: Preoperative tumor localization and differentiation between adenoma and hyperplasia. N Engl J Med 286:1169-1175, 1972

Will Private Medicine Self-Destruct?

WILL PRIVATE MEDICINE SELF-DESTRUCT? This would have been an unthinkable question only a few months ago. Now it is not. Practicing physicians are under unprecedented stress and their behavior under this stress is being carefully watched by their patients and the public. The stress is undeniably intense. Many physicians, perhaps a majority in California, face the imminent likelihood that they will not be able to get malpractice insurance at a price they can reasonably afford to pay, or perhaps at any price. If they continue their practice without any insurance they do so at great personal financial risk, and if they quit practice they find themselves suddenly cut off both from their life's work, which is the care of patients, and from their income. As more and more physicians come to face this really terrible personal dilemma, tension understandably mounts. And born of this frustration, there now has been a call from some within the profession for a massive strike of protest.

A strike by physicians is not an ordinary strike. It has far more than ordinary potential for harm and for backlash. In such a situation each physician should begin by asking himself exactly what will be accomplished—for himself, for his patients or for his profession—and then decide what his stance will be. Who will be affected by a strike to protest high malpractice insurance premiums and how will they be affected? It seems unlikely that the malpractice insurance carriers will quickly lower their rates, so an immediate solution to the problem with direct and immediate benefit to the physician seems unlikely. The public is already aware of and generally sympathetic to the doctors' malpractice plight. The real effect of a massive doctor's strike would be first on patients, then on the private sector of medicine itself and finally on all physicians by way of a predictable counterreaction by the public. The adverse effect on patients is obvious enough. But experience shows that private hospitals and even physicians' private offices are extremely vulnerable to the financial ramifications of a work stoppage by doctors. All of this could only be destructive. We actually could pull our house down with us. Finally, the public views medical services as essential to protection much as are the services of firemen and the police, and there is good recent evidence that the public does not take kindly to the interruption of these kinds of services by strikes.

These are times when medicine needs to gain strength and stature and not lose it, or worse, be punished by the public perhaps even at the polls as was the recent fate of striking firemen and policemen in San Francisco. These are times when physicians should approach their own stressful practice problem the same way they would approach a difficult and stressful patient care problem. Physicians do not panic when they are taking care of patients, nor do they protest or run away. When the going is tough they keep a steady hand and work the problem through, always doing what they believe is best for their patients in the highest traditions of the profession. This is exactly the approach that is needed now. The public expects physicians to deal with their practice problem in the same professional manner in which they would handle a complex and frustrating problem in patient care. If we do this now, in ways that all can see, the profession will gain in strength, stature and influence. If we do not we might even manage to self-destruct private medicine.

—MSMW

CASE REPORTS

Refer to: Von Hoff DD, Luckey M, Wallace J, et al: Herpes type 2 meningitis following herpes progenitalis. West J Med 123:490-491, Dec 1975

Herpes Type 2 Meningitis Following Herpes Progenitalis

DANIEL D. VON HOFF, MD
MARJORIE LUCKEY, MD
JEANNE WALLACE, MD
FAITH FITZGERALD, MD
San Francisco

CULTURE OF herpesvirus hominis type 2 from cerebrospinal fluid of adult patients with aseptic meningitis has been reported sporadically.[1-3] Herpesvirus hominis type 2 infections of the central nervous system in association with herpes progenitalis have also been observed but more rarely.[4,5] A case of herpesvirus hominis type 2 meningitis after herpes progenitalis is reported in which the cerebrospinal fluid level of protein is the highest reported to date.

Report of a Case

A 28-year-old woman was admitted to Moffitt Hospital on October 13, 1974 because of sudden onset of severe low back pain without dysuria, followed by headache, fever, shaking chills, meningismus, ocular pain on downward gaze and lethargy. Three days previously, vesicular vulvar lesions developed and were diagnosed by a gynecologist as genital herpes; a single application of neutral red with photo inactivation was associated with symptomatic relief. The patient had no history of herpes infection but had been exposed to culture-proved tuberculosis two months earlier.

On physical examination temperature was 40°C (104°F), blood pressure 110/68 mm of mercury and pulse 120 per minute. Pertinent findings included bilateral tender inguinal adenopathy, multiple crusted vulvar lesions on erythematous bases with a normal appearing cervix and meningismus with positive Brudzinski's and Kernig's signs. There was no tenderness in the costovertebral angle, no skin or oral lesions, no ocular lesions and no abnormalities in sensory, motor and cerebellar function. Cranial nerves were intact. Laboratory data included a leukocyte count of 8,300 per cu mm with 75 percent polymorphonuclear cells, 15 percent lymphocytes and 10 percent monocytes; hematocrit 42 percent; sedimentation rate 13, and normal levels of serum electrolytes, creatinine and blood urea nitrogen. Results of urinalysis were within normal limits, and Venereal Disease Research Laboratories (VDRL) and purified protein derivative (PPD, intermediate strength), and mumps skin tests gave negative results. Roentgenograms of chest, skull, sinuses, cervical spine and lumbosacral spine showed no abnormalities.

Admission lumbar puncture was carried out and the cerebrospinal fluid showed leukocytosis (mostly lymphocytes), elevated protein and borderline glucose levels (Table 1). Because of these values and the patient's rigors, intravenous ampicillin therapy was started, pending routine culture results. Isoniazid, ethambutal and streptomycin were added to the regimen because of the documented exposure to tuberculosis two months previously.

Repeat lumbar puncture on day two showed an increase in protein level to 379 mg per 100 ml (Table 1). The patient continued to be lethargic and fever, nausea and vomiting were present. Findings on all routine cultures of blood and cerebrospinal fluid were negative, as were India ink and acid-fast bacilli stains and cytologic studies. Administration of ampicillin was discontinued, but antituberculous therapy was maintained. On day three the patient became afebrile, meningismus decreased and the cerebrospinal fluid level of protein declined. The patient improved symptomatically, and lumbar puncture on day five showed resolution of cerebrospinal fluid abnormalities.

On day six, viral cultures of cerebrospinal fluid obtained on day two showed cytopathic changes;

From the Medical Service, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco.

Submitted April 14, 1975.

Reprint requests to: Daniel D. Von Hoff, MD, Department of Medicine, University of California, San Francisco, CA 94143.

herpesvirus hominis type 2 was subsequently isolated. Viral cultures of the genital lesions failed to grow herpesvirus, probably because the lesions had already crusted over. Unfortunately, no buffy coat cultures were obtained. Antituberculous medications were discontinued, and the patient was discharged. About one month after discharge, recrudescent meningismus and symptoms coincident with reappearance of labial herpetic lesions occurred. The patient refused lumbar puncture or labial lesion cultures and recovered without complication on bed rest alone. No further episodes have occurred. No oral or ocular lesions suggestive of Behçet's syndrome were ever evident.

Discussion

This case represents a culture-proved herpesvirus hominis type 2 meningitis. It is of interest because of the pronounced lymphocytosis and the very high protein levels in the cerebrospinal fluid and because of its association with herpes progenitalis infection. The initial symptom of sudden severe lumbarsacral spine pain is of interest in light of reports of ascending myelitis with herpes simplex virus (herpesvirus hominis type 1)[6] and the recent observations of Baringer[7] of herpesvirus hominis type 2 cultured from presacral ganglia of autopsied patients. One could speculate that the herpesvirus hominis type 2 in our patient traveled via the presacral ganglia to the central nervous system via a direct neural route rather than a hematogenous route as suggested by Craig and Nahmias.[2]

The genital lesions of our patient were treated with neutral red. Photodynamic inactivation of genital herpes infections with the heterotricyclic dyes proflavin or neutral red has been used as a therapeutic approach.[8-10] Recently, however, there has been some evidence to suggest that photodynamic inactivation may change the herpesvirus in such a way as to make it carcinogenic.[11] There is increasing reluctance to use photoinactivation therapy because of this evidence.

TABLE 1.—*Results of Analyses of Cerebrospinal Fluid Obtained by Serial Lumbar Punctures**

	Date 1974			
	10/13	10/14	10/15	10/17
	8 pm	1 am	2 pm	4 pm
Opening pressure mm Hg	273	150	230	180
Leukocytes				
Count/mm³	510	740	1,250	583
Polymorphonuclear (percent)	11	18	4	..
Lymphocytes (percent)	80	81	59	..
Eosinophils (percent)	5	1	1	..
Pia-arachnoid (percent)	..	..	34	..
Basophils (percent)	..	..	1	..
Red blood cells/mm³	60	80	400	42
Protein mg/100 ml	293	379	196	76
Glucose mg/100 ml	42	42	82	48
Blood	89	106	186	89
Cultures				
Routine	neg	neg	neg	neg
Acid-fast bacilli	neg	neg	neg	neg
Fungal	neg	neg	neg	neg
Viral	..	pos†	..	..

*In addition, findings on histoplasmin, cryptococcal and coccidioidomycosis complement fixation tests were all negative.
†Positive for herpesvirus hominis type 2.

Summary

Herpesvirus hominus type 2 was isolated from the cerebrospinal fluid of a woman with aseptic meningitis who recently had a herpes progenitalis infection. The meningitis was associated with an extremely high level of protein (379 mg per 100 ml) and extreme lymphocytosis in the cerebrospinal fluid.

ADDENDUM: Since the paper was submitted, the patient has had several recrudescences of the disease and has had to be admitted to hospital twice. On both of those occasions, cerebrospinal fluid, while showing moderate to minimal pleocytosis, normal sugar and normal protein, has been culture sterile for herpes type 2. During each exacerbation clinical features have been present compatible with a demyelinating disorder, including multifocal sensory and motor neurologic signs of both peripheral and cranial distribution. While there has been a definite temporal association between the recrudescence of the labial herpes and the meningitic, now encephalitic, episodes, it is not clear that we are dealing with an infectious process in relapse. Possibilities include an underlying demyelinating disorder or a postinfectious demyelinating syndrome which is unique in its resolution and relapse pattern. The patient currently is being treated with high doses of steroids and some clinical resolution is being seen.

REFERENCES

1. Morrison RE, Miller MH, Lyon LW, et al: Adult meningoencephalitis caused by herpesvirus hominis type 2. Am J Med 56: 540-544, 1974
2. Craig CP, Nahmias AJ: Different patterns of neurologic involvement with herpes simplex virus type 1 and 2—Isolation of herpes simplex virus type 2 from the buffy coat of two adults with meningitis. J Infect Dis 127:365-372, 1973
3. Armstrong C: Herpes simplex virus recovered from spinal fluid of suspected case of lymphocytic choriomeningitis. Public Health Rep 58:16-21, 1943
4. Terni M, Caccialanza P, Cassai E, et al: Asceptic meningitis in association with Herpes progenitalis. N Engl J Med 285:503-504, 1971
5. Sköldenberg B, Jeansson S. Wolontis S: Herpes simplex virus type 2 in acute aseptic meningitis. Br Med J 2:611, 1973
6. Klastersky J, Cappel R, Snoeck JM, et al: Ascending myelitis in association with herpes-simplex virus. N Engl J Med 287: 182-184, 1972
7. Baringer JR: Recovery of herpes simplex virus from human sacral ganglions. N Engl J Med 291:828-830, 1974
8. Kaufman RH: Dye, then light, ease virus symptoms. JAMA 226:528, 1973
9. Friedrich EG Jr: Relief for herpes vulvitis. Obstet Gynecol 41:74-77, 1973
10. Weinstein L, Chang T-W: The chemotherapy of viral infections. N Engl J Med 289:725-730, 1973
11. Rapp F, Li JL, Jerkofsky M: Transformation of mammalian cells by DNA-containing viruses following photodynamic inactivation. Virology 55:339-346, 1973

Refer to: Glauser FL, Smith WR: Far-advanced pulmonary interstitial disease with normal findings on a chest radiograph. West J Med 123:492-495, Dec 1975

Far-Advanced Pulmonary Interstitial Disease with Normal Findings on a Chest Radiograph

FREDERICK L. GLAUSER, MD
Long Beach

WILLIAM RICHARD SMITH, MD
Irvine

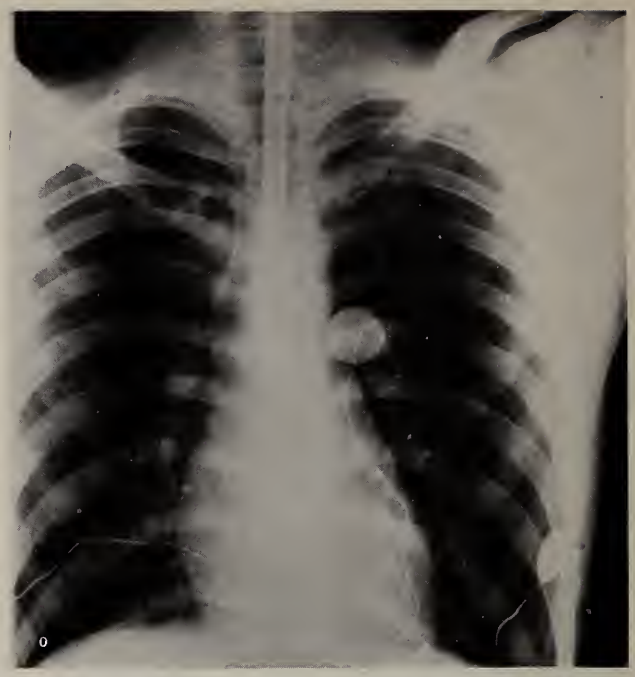


Figure 1.—Admission chest radiograph. Note clear lung fields. Diaphragm below level of 11th rib posteriorly. Gastric tube in place.

DIFFUSE INTERSTITIAL LUNG DISEASE is suspected in a tachypneic patient with end inspiratory pulmonary rales and the following abnormalities of pulmonary function: reduced vital capacity, total lung capacity and diffusing capacity in the presence of normal flow rates. A radiograph of the chest usually shows diffuse interstitial abnormalities.[1] Depending on the specific disease, all measurements may not parallel one another in an individual case. For example, idiopathic intersitial fibrosis may be suspected because of abnormal findings on a routine chest radiograph, yet in such patients symptoms may not be present and results on physical examination may be within normal limits.[2] In contrast, patients with sarcoid may present with hilar adenopathy and normal lung parenchyma shown by chest radiograph, while pulmonary function studies usually show a decreased diffusing capacity consistent with diffuse interstitial pulmonary involvement by granuloma or fibrosis or both.[3] This disparity is usually presumed to be secondary to an intersitial process undetectable by routine radiograph. However, it is not generally appreciated that, in other conditions, interstitial lung disease may occur with essentially normal findings on a chest radiograph.

Recently, we observed a young patient, with previously normal lungs, in whom there was acute onset and rapid progression of pulmonary fibrosis secondary to the ingestion of paraquat (a toxic herbicide).[4] In this case we documented rapid progression (by pulmonary function testing) of a process compatible with severe interstitial edema or fibrosis or both while the findings on routine chest radiograph remained normal.

Report of a Case

A 16-year-old white boy ingested a mouthful of paraquat in a suicidal gesture at 8:30 a.m. He was admitted to the emergency room at 9:00 a.m. and gastric lavage with tap water and milk through a large bore gastric tube was carried out. Results of physical examination were normal except for a respiratory rate of 28 per minute. Findings on studies of blood gases (fraction of inspired oxygen [F_IO_2] 0.21) showed an arterial oxygen pressure (PaO_2) of 122 mm of mercury, an arterial carbon dioxide pressure ($PaCO_2$) of 19 mm of mercury (alveolar arterial oxygen difference [$A\text{-}aO_2$] gradient of 8 mm of mercury) and a pH of 7.56. Results of a chest radiogram (Figure 1) were normal. The therapeutic regimen, which continued throughout the patient's hospital course, was as follows: (1) low F_IO_2 to maintain his PaO_2 at approximately 50 mm of mercury (since oxygen enhances the toxicity of paraquat), (2) forced diuresis up to 10 liters per day, (3) daily

From the Department of Medicine, University of California, Irvine, California College of Medicine, Irvine.

Submitted, revised, June 16, 1975.

Reprint requests to: Frederick L. Glauser, MD, Pulmonary Section B, Veterans Administration Hospital, 5901 East Seventh Street, Long Beach, CA 90801.

TABLE 1.—*Findings on Sequential Upright Pulmonary Function Test and Arterial Blood Gas Studies*

	Hospital Day								Predicted Values
	2	3	4	5	8	12	16	23	
Vital capacity* (VC)	3.19	2.85	..	1.15	1.55	1.75	1.51	..	5.60
Alveolar volume* (V_A)	5.09	3.99	2.50	2.35	2.89	2.97	2.42	..	6.70
Diffusing capacity† (DLCO)	39.40	..	18.00	19.00	10.00	8.30	7.50	..	38.70
F_IO_2	0.15	0.14	0.15	0.15	0.17	0.17	0.21	0.60	0.21
PaO_2‡	51.00	46.00	48.00	48.00	42.00	44.00	44.00	50.00	>85
$PaCO_2$‡	24.00	24.00	25.00	26.00	29.00	30.00	28.00	32.00	38-42
A-aO_2‡ gradients	31.00	30.00	34.00	33.00	50.00	47.00	77.00	346.00	<10

*liters based upon height and age
†ml/min/mmHg
‡mmHg

F_IO_2=fraction of inspired oxygen
PaO_2=arterial oxygen pressure
$PaCO_2$=arterial carbon dioxide pressure
A-aO_2=alveolar arterial oxygen difference

Figure 2.—Chest radiograph on fifth hospital day. Lung fields clear except for the possibility of a left sided retrocardiac infiltrate. Diaphragm above 10th rib posteriorly. Vital capacity 2.85 liters; alveolar volume 3.99 liters.

ultrafiltration hemodialysis, (4) intravenously given hydrocortisone, 1 gram daily, (5) d-propranolol and superoxide dismutase (experimental drugs which combat the toxic effects of paraquat).

The usual toxic effects associated with paraquat were seen: (1) acute renal failure, (2) hepatic involvement, (3) cardiac arrhythmias, (4) gastrointestinal irritability and bleeding.

On the second hospital day bedside upright pulmonary function studies were obtained as noted in Table 1. Both the vital capacity (VC, as determined by spirometry) and alveolar volume (V_A, as determined by neon) were 70 percent of predicted even though the single breath diffusing capacity for carbon monoxide (DLCO) was normal.[5] By the third hospital day VC, V_A and DLCO were 50 percent of predicted. On a radiograph of the chest clear lung fields were noted (except for a questionable retrocardiac density on the left), however, the diaphragm was elevated. By the fifth hospital day VC and V_A were 20 percent of predicted and the DLCO 50 percent of predicted. Findings on chest radiographs remained unchanged (Figure 2). In addition, during this time, the A-aO_2 gradient had increased to 30 to 33 mm of mercury (Table 1).

On the eighth hospital day alveolar infiltrates were noted in the left lower lobe by chest radiograph (Figure 3), the patient was more dyspneic and the A-aO_2 gradient was worsening (Table 1). Vigorous diuresis led to minimal improvement in the chest radiograph with concomitant increases in the VC and V_A but not the DLCO (Table 1). The patient's course was inexorably downhill as increasing amounts of supplemental oxygen were required and he died on the 22nd hospital day.

Results of a limited autopsy showed no gross pathologic alteration in any organ system except for the lungs which were described as follows: the right and left lungs weighed 1,000 grams each and were notably firm to palpation. On sectioning of the lungs, a mottled purplish-red cut surface was seen which was notably firm to palpation. On microscopic examination, diffuse, extensive, far advanced pulmonary fibrosis was found with areas of intraalveolar hemorrhage (Figure 4).

Discussion

Clinically, diffuse interstitial lung disease is suspected by findings on physical examination and pulmonary function testing, but this diagnosis is not seriously entertained unless the classic abnormalities are noted on a radiograph of the chest.[2] Thus, most clinicians and radiologists would seem to place undue significance on the results of a chest radiograph. Strong emphasis on

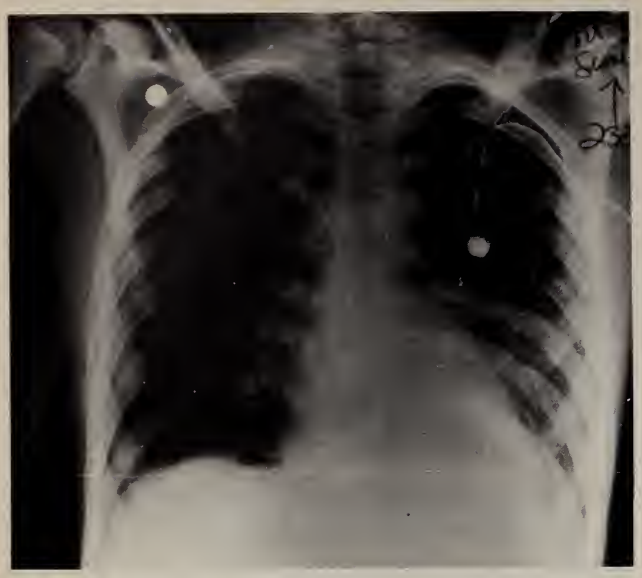


Figure 3.—Chest radiograph on eighth hospital day. Alveolar infiltrate left lower lobe. Minimal infiltrate right lower lobe. Vital capacity 1.55 liters; alveolar volume 2.89 liters; single breath diffusing capacity for carbon monoxide (DLCO) 10 ml per minute per mm of mercury.

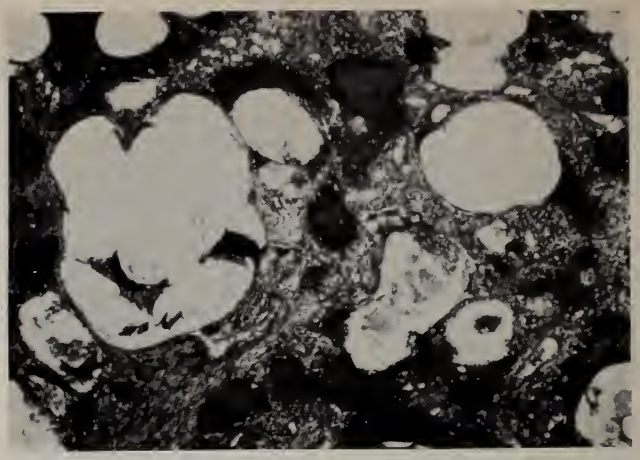


Figure 4.—Histology of the lung showing extensive, far advanced, diffuse pulmonary fibrosis.

findings from a chest radiograph may be correct in many situations, but, as shown by the present case, advanced interstitial lung disease (evidenced by typical abnormalities of pulmonary function) may only be manifested on an upright chest radiograph by elevated diaphragm. These findings are not totally unique since others have reported pulmonary fibrosis in the presence of normal findings on chest radiographs.[6,7]

Unger and co-workers[8] are aware of the paradox of a normal chest radiograph in patients with moderate to severe pulmonary symptoms. In a treatise dealing with hypersensitivity pneumonitis they state, "It is both surprising and disconcerting to the radiologist to be confronted with a patient with moderate to severe pulmonary symptoms without any demonstrable findings on the chest film. Because of the increasing awareness of these diseases, we will probably see more of these early patients with normal film. This fact, although well known to the allergist, does not seem to have been stressed sufficiently in the radiologic literature."

It might be argued that since we did not have tissue proof early in the course of our patient's disease (that is, when findings on chest radiographs were essentially normal while pulmonary function studies gave results compatible with severe restrictive disease) that interstitial disease was indeed not present and the decreased lung volumes shown both by radiographs and pulmonary function studies were due to poor patient cooperation. That this thesis is probably invalid may be surmised from several pieces of evidence: (1) The changes in lung volumes were consistently in one direction (worsening) and once they reached their minimum values tended to remain that way (Table 1). Poor patient cooperation usually produces fluctuating alterations in pulmonary functions both increasing and decreasing in a variable and unpredictable manner. Since all tests were carried out in the upright position, the effects of changes in posture on the pulmonary function tests were avoided. (2) The DLCO was much lower than would be expected just from a self-induced decrease in lung volumes. (3) The chest radiographs and pulmonary function tests, both of which showed loss of lung volume, were done at separate times during the day. Both showed changes always consistent with loss of lung volume.

In paraquat poisoning in both animals and humans, interstitial fibrosis has been noted as early as the third to fifth day after ingestion.[9-12] In our patient, changes in pulmonary function studies occurred at appropriate times.

In conclusion, our case suggests that relatively far advanced diffuse interstitial lung disease may be shown on chest radiographs only as loss of lung volumes, evident as an elevated diaphragm. In symptomatic patients in whom the diaphragm is persistently elevated with normal lung fields, pulmonary function testing may help define the clinical situation.

Summary

A case of rapidly developing and fatal pulmonary fibrosis is reported in a 16-year-old boy. At

a time when findings on pulmonary function tests were compatible with severe interstitial lung disease, a radiograph of the chest showed clear lung fields, but elevated diaphragm. The insensitivity of routine radiographs of the chest in reflecting the pathologic changes in certain cases of far advanced pulmonary interstitial disease is underscored by this case.

REFERENCES

1. Bates DV, Macklem PT, Christie RV: Respiratory Function in Disease. Philadelphia, WB Saunders Co., 1971, pp 268-286

2. Fraser RG, Pare JAP: Diagnosis of Diseases of the Chest. Philadelphia, WB Saunders Co., 1971, pp 187-319

3. Young RC, Carr C, Shelton TG et al: A radiologic approach to hypersensitivity pneumonias. Am Rev Respir Dis 95:224-238, 1967

4. Fisher HK, Clements JA, Bails R: Paraquat poisoning: Recovery from renal and pulmonary damage. Ann Intern Med 75: 731-736, 1971

5. Cotes JE: Lung Function. Philadelphia, FA Davis Co., 1968, pp 208-260

6. Tranquada R, Simmons D, Miller J: Pulmonary fibrosis in scleroderma. Arch Intern Med 105:607-611, 1960

7. Williams MH, Adler JJ, Colp C: Pulmonary function studies as an aid in the diagnosis of pulmonary hypertension. Am J Med 47:378-383, 1969

8. Unger GF, Scanlon GT, Fink JN, et al: A radiologic approach to hypersensitivity pneumonias. Radiol Clin North Am 11: 339-356, 1973

9. Davidson JK, MacPherson P: Pulmonary changes in paraquat poisoning. Clin Radiol 23:18-25, 1972

10. Fisher HK, Clements JA, Wright RR: Pulmonary effects of the herbicide, paraquat, studied 3 days after injection in rats. J Appl Physiol 35:268-273, 1973

11. Modee J, Iremark BI, Robertson B: Ultrastructure of the alveolar wall in experimental paraquat poisoning. Acta Pathol Microbiol Scand 80:54-60, 1972

12. Murray RE, Gibson JE: Comparative study of paraquat intoxication in rats, guinea pigs, and monkeys. Exp Mol Pathol 17:317-325, 1972

"Breath-Holding" Spells

A very common condition is the breath-holding spell which does not begin with a "holding-of-breath." This is a very poor term. Children do not hold their breath in inspiration when they have a breath-holding spell; they expire the breath and do not take a second breath. And this is very important in getting the history, because if you ask most mothers if the child holds his breath, the mother will imagine in her mind a child going "Aaah, I'm holding my breath!" when actually the child expires breath and never takes the next breath. I rarely use the term breath-holding, but will ask the mother to describe what has happened in the greatest of detail. Indeed, you will find that the child has cried or has been annoyed or in some way has been disturbed and has just stopped breathing—has not taken the next inspiration—and then turns blue. He may just pass out or may go on and have a convulsion. A convulsion with a breath-holding spell, or "not-breathing" spell, does not make it any less a breath-holding spell. Medication will not prevent that kind of convulsion. The child will convulse if he gets anoxic enough, whether or not diphenylhydantoin (Dilantin®) or phenobarbital is used, just as a child whose blood sugar drops from too much insulin will convulse, whether or not you use phenobarbital or Dilantin. These types of stresses cannot be prevented with anticonvulsant medication and should not be treated as such. The only cure I know for breath-holding spells, which are of course temper tantrums, is a very difficult one—the total ignoring of the spell.

Children never have spells without an audience and it is imperative that the mother or whomever else the child has the spells for—and it is usually a small number of people for whom a child will have breath-holding spells—leaves the room completely, without peeking through a curtain, while this episode is going on. The child has to wake up and find that he has gone through this enormous act without any audience. After one or two times, the child will invariably stop doing it. It is very difficult, however, to get parents to leave a child during a breath-holding spell.

—GERALD M. FENICHEL, MD, *Nashville*

Extracted from *Audio-Digest Pediatrics*, Vol. 21, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057

LETTERS *to the Editor*

Sjögren's Syndrome with Light Chain Myeloma

To the Editor: Sjögren's syndrome, a chronic inflammatory multisystem disease with autoimmune aspects, is characterized by dryness of the eyes and mouth. Rheumatoid arthritis, systemic lupus erythematosus or another rheumatic disorder is frequently associated with this disease.[1]

Malignant lymphoma and Waldenström's macroglobulinemia occur with increased frequency in patients with Sjögren's syndrome.[2] When the associated disorders have been monoclonal, they have uniformly involved immunoglobulin M (IgM).[3] The following case represents the first instance, as far as we are aware, of light chain myeloma developing in a patient with Sjögren's syndrome.

A 71-year-old white woman presented with a history of dry eyes, dry mouth and polyarthralgia of 20 years' duration, in association with a nonproductive cough and increasing dyspnea on exertion. The physical examination revealed inflamed conjunctivae, a dry mouth with deeply fissured tongue, and rhonchi and dry rales in posterior lung bases bilaterally. Significant laboratory values included hemoglobin, 11.2 grams per 100 ml; leukocyte count, 8,100 per cu mm with normal differential count; erythrocyte sedimentation rate, 61 mm per hour (Westergren); rheumatoid factor (Latex®), 1:160; antinuclear antibody test positive with diffuse pattern. The urine contained 2 plus protein with normal sediment. A 24-hour specimen of urine contained 2.6 grams of protein. Creatinine clearance (corrected) was 56 ml per minute. Serum electrophoresis showed normal albumin with diffuse increase in γ-globulins. Immunoelectrophoresis of serum proteins showed immunoglobulin G (IgG), 2.26 grams; immunoglobulin A (IgA), 0.04 grams; IgM, 0.07 grams per 100 ml. Electrophoresis of the urine showed a spike in the β-γ region representing virtually all of the urine protein. The spike consisted of free λ-chains. Result of the heat test for Bence Jones protein in the urine was positive. Findings on tests for Sjögren's syndrome were all strongly positive; labial biopsy was confirmatory.[3]

Radiograph of the chest showed densities in a honeycomb pattern in the lower lung fields, suggestive of chronic interstitial pulmonary fibrosis. Pulmonary function studies showed a restrictive pattern.

The bone marrow aspirate was consistent with multiple myeloma; there was plasmacytosis in excess of 15 percent, with numerous clusters of immature-appearing plasma cells. Bone survey showed diffuse osteoporosis but no lytic lesions. Amyloid was not seen on biopsy of the lip and rectal mucosa.

Peripheral blood T lymphocytes, measured by rosette assay with sheep erythrocytes, were reduced to 44 percent (normal, 71 percent $\pm$ 5 percent). B lymphocytes, measured by direct immunofluorescence with polyvalent immunoglobulins after overnight culture, were decreased to 5 percent (normal, 12 percent $\pm$ 2 percent).

Although the vast majority of cases of Sjögren's syndrome remain benign, an enhanced risk of developing a lymphoproliferative disorder is associated with this condition. Patients who exhibit evidence of extension of lymphoid infiltrates from the usual glandular locations to extraglandular sites such as lung, kidney, bone marrow or lymph nodes are considered to have pseudolymphoma, a stage intermediate between benign disease and malignant lymphoma. Such patients also often show depression of peripheral T lymphocytes and evidence of decreased cellular immunity.[4] The patient reported here manifested findings of chronic interstitial pulmonary fibrosis, one of the clinical features that may characterize the group with pseudolymphoma; she also displayed depression of blood T lymphocytes. These findings are consistent with the fact that her disease process was of a relatively aggressive type, and placed her at greater risk of developing malignant lymphoma.

A current concept regarding the pathogenesis

of Sjögren's syndrome suggests that there is a deficiency of T suppressor lymphocytic activity, leading to uncontrolled proliferation of B lymphocytes, which usually induces polyclonal hypergammaglobulinemia.[3] The only monoclonal malignant disorder observed in Sjögren's syndrome heretofore has been Waldenström's macroglobulinemia.

The development of myeloma in the setting of Sjögren's syndrome is unusual. At the present time it is not known whether nonlymphatic malignant neoplasias occur more commonly in Sjögren's syndrome than in the general population. Thus, the coexistence of these two relatively uncommon disorders may merely represent chance association. As an alternative possibility, depressed immune surveillance secondary to the immunologic aberrations noted in this patient could have played a role in the emergence of the malignant neoplastic disease.

MARTIN A. SHEARN, MD
Departments of Medicine
Kaiser-Permanente Medical Center
Oakland, California; and
University of California, San Francisco,
School of Medicine

HARALAMPOS M. MOUTSOPOULOS, MD
Department of Medicine
University of California, San Francisco,
School of Medicine; and
Section of Clinical Immunology and Rheumatology
Veterans Administration Hospital
San Francisco

SHIGEWASA SAWADA, MD
Section of Clinical Immunology and Rheumatology
Veterans Administration Hospital
San Francisco

CARL GAK, MD
Department of Medicine
Kaiser-Permanente Medical Center
Oakland, California

REFERENCES

1. Shearn MA: Sjögren's Syndrome. Philadelphia, W. B. Saunders Company, 1971

2. Anderson LG, Talal N: The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. Clin Exp Immunol 10: 199-221, 1972

3. Recent clinical and experimental developments in Sjögren's syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 122:50-58, Jan 1975

4. Talal N, Sylvester RA, Daniels TE: T and B lymphocytes in peripheral blood and tissue lesions in Sjögren's syndrome. J Clin Invest 53:180-189, 1974

Travelers' Diarrhea and Others

TO THE EDITOR: Two recent articles appearing in the JOURNAL about diarrheal diseases contain statements that are misleading (Cronin C: Enteropathogenic escherichia coli (EPEC) in infants and travelers' diarrhea, *In* Important Advances in Clinical Medicine: Epitomes of Progress—General and Family Practice. West J Med 121: 317-318, Oct 1974 and St Geme JW Jr: Seminars in infectious disease—A new look at infectious gastroenteritis. West J Med 121:456-461, Dec 1974). I would like to comment.

Contrary to Dr. Cronin's recommendation, in my opinion, evidence suggests that "turista" or travelers' diarrhea should not be treated with diphenoxylate hydrochloride with atropine sulfate (Lomotil®). DuPont and Hornick have described adverse effects of Lomotil therapy in treatment of shigellosis. Also Gangarosa states that his findings persuade him that Lomotil and other drugs that decrease gastrointestinal motility should not be used in the general prevention or treatment of travelers' diarrhea. These drugs, he states, seem to prolong the illness and may be very dangerous to a traveler suffering from diarrhea due to any acute intestinal infection. The recommendation to a traveler suffering from "turista" should be to replace lost fluids by whatever means are most feasible. The various electrolyte-glucose preparations (such as Choloral® marketed by Vifor, a Swiss Company) are excellent; if they are not available one might use fruit juice or sweetened tea. Iodochlorhydroxyquin (Entero-Vioform®) seems not to change the illness and indeed may be harmful and confuse the diagnosis. The role of antibiotics in prevention is still unclear. Antibiotics prolong salmonellosis but help in shigellosis. Fever should warn the patient to see a physician.

Dr. St. Geme mentions that the Norwalk agent (1) was isolated from an outbreak in Norwalk, Connecticut, (2) looms as the principal cause of acute infectious nonbacterial gastroenteritis (AING) and (3) has been observed to be present in 80 percent of Australian children from Melbourne with sporadic AING. Actually the Norwalk agent was recovered from an outbreak of AING that developed in 50 percent of the students attending an elementary school in Norwalk, Ohio, in October 1968. The agent has been studied extensively since and is now considered an important cause of AING; however, in recent years

another agent has been discovered that is also associated with epidemics of AING. This latter agent is very different from the Norwalk agent and is the agent responsible for AING in approximately 75 percent of children in Melbourne, Australia. It has been called duovirus, rotavirus, orbivirus or the reovirus-like agent. One reason for its many names is that many observers in at least nine countries have "recently discovered" this agent as a major cause of AING in children less than six years old. The point to be made, I believe, is that because of recent advances in visualization of fecal viruses and in viral culturing methods, agents associated with AING will be found and many of the etiological mysteries of the heretofore acute diarrheal illness of unknown cause will be solved. Currently other viral agents including a coronavirus are being described as a cause of sporadic cases of acute diarrhea.

RICHARD N. GREENBERG, MD
Epidemic Intelligence Service Officer
Center for Disease Control, New Orleans

BIBLIOGRAPHY

Dupont HL, Hornick RB: Adverse effect of Lomotil therapy in shigellosis. JAMA 226:1525-1528, 1973

Merson MH, Gangarosa EJ: Travelers' diarrhea. JAMA 234: 200-201, 1975

Kean BN, Gangarosa EJ: Dealing with food poisoning. Medical World News 16:74-83, 1975

Merson MH: Toxigenic turista. N Engl J Med 292:969-970, 1975

Blacklow NR, et al: Acute infectious nonbacterial gastroenteritis: etiology and pathogenesis. Ann Intern Med 76:993-1008, 1972

Davidson GP, et al: Importance of a new virus in acute sporadic enteritis in children. Lancet 1:242-245, Feb 1, 1975

Rotaviruses of man and animals. Lancet 1:257-259, Feb 1, 1975

Almeida JD: Visualization of fecal viruses. N Engl J Med 292: 1403-1404, 1975

BOOK REVIEW

ADVANCES IN PRIMARY CARE—Conference Proceedings in Honolulu, Hawaii February 16-22, 1974— Edited by Marta C. Kallstrom, and Stephen R. Yarnall, MD, President of Medical Computer Services Association, Seattle. Medical Computer Services Association, 1107 N.E. 45th Street, Seattle (98105), 1974. 195 pages, $16.00 (paperback).

Advances in Primary Care is a collection of papers presented at a conference in Honolulu, Hawaii in February 1974.

There has been little apparent attempt on the part of the editors to select or edit these papers. The quality and content of the papers are variable and there is little cohesiveness. Many of the papers are descriptions of innovations in health care that have been widely described in medical literature for the past several years, innovations such as the problem-oriented record, and automated multiphasic health testing.

The papers generally lack a bibliography, and therefore would provide little help to a student attempting to research the topic presented.

Some of the papers are brief descriptions of problems which relate to a specific geographical area and contain no suggestions for solution.

In summary, I do not see this as a monograph, but rather as a disjointed collection of papers of varied quality, which are perhaps of some value to the student seeking to review some of the advances in health care delivery.

RAYMOND C. ANDERSON, MD

Trauma Rounds

Chief Discussant
NORMAN CHRISTENSEN, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Christensen N: Injuries to duodenum, small intestine and mesentery (Trauma Rounds). West J Med 123:499-502, Dec 1975

Injuries to Duodenum, Small Intestine and Mesentery

PETER NOYES, MD:* The case for discussion today is that of a 24-year-old white man who presented with a stab wound of the abdomen. On initial examination, the patient appeared otherwise healthy and seemed to have minimal abdominal pain. There was a single 2 cm laceration of the right lower abdominal quadrant midway between the pubis and the umbilicus along the lateral border of the rectus muscle. There was some right lower quadrant abdominal tenderness. The blood pressure was 130/70 and pulse 80. The hematocrit was 43, and leukocyte count 10,300 with a normal differential.

Venous lines, one of which was a central venous pressure line, were placed in each upper extremity. Administration of Ringer's lactate was started and a Foley catheter was inserted.

The patient's condition remained stable and he was taken to the operating room one hour later. The abdomen was explored through a long midline incision. Approximately 400 ml of blood was noted to be present within the peritoneal cavity. After thorough exploration, two 1 cm longitudinal wounds of a loop of midjejunum and a 2 cm laceration of the mesentery were discovered. In addition, there was an 8 cm hematoma of the mesentery opposite another bowel laceration 20 cm distal to the first area of injury. Two proximal bowel lacerations were closed using interrupted nonabsorbable sutures. The segments of bowel and mesentery containing the hematoma were resected and an end-to-end open two-layer anastomosis carried out. The patient had an uneventful postoperative course and was discharged from the hospital on the sixth postoperative day.

F. WILLIAM BLAISDELL, MD:† *Dr. Christensen, I would like to ask you to comment on the management of injuries of the small bowel and mesentery.*

NORMAN CHRISTENSEN, MD:‡ The treatment of these injuries is generally straightforward but large wounds; avulsions of the mesentery from the intestine; blunt, multiple and duodenal injuries may present problems that tax surgical judgment. The high morbidity and mortality that follow large bowel injuries is not seen with injuries of the small intestine. Leakage from suture lines is rare. During World War II in soldiers, the leakage rate from sutured lacerations of the small intestine was approximately 1 percent. It is undoubtededly much less in civilian practice. On the other extreme, duodenal injuries are the most difficult of all gastrointestinal injuries to manage. They may be overlooked or, if identified, improperly treated—setting the scene for development of a duodenal fistula with its disastrous consequences. The mortality rate for duodenal injuries is between 10 and 15 percent. One of the reasons

*Senior Resident, Trauma Service, San Francisco General Hospital.
Reprint requests to Donald Trunkey, MD, Department of Surgery, San Francisco General Hospital, San Francisco, CA 94110.

†Chief, Surgical Service, San Francisco General Hospital.
‡Visiting clinical Professor of Surgery, San Francisco General Hospital.

for such a high mortality rate is associated injury of nearby vital structures.

At the operating table our object is to control hemorrhage, close all perforations and remove all dead bowel. The small intestine should be eviscerated and the bowel and its mesentery carefully examined from the ligament of Treitz to the ileocecal valve. The large intestine and duodenal loop should be examined at the same time. The surgeon should count the number of perforations of the intestine. An odd number of perforations must be explained, since failure to do so may mean missing another perforation. Usually the missed perforation will lie on the mesenteric side of the bowel. Missiles can cause tangential wounds, resulting in only one perforation of the bowel, and knives or other sharp objects may penetrate only one wall of the bowel. However, most perforating wounds involve both bowel walls. Therefore, it is essential, if an odd number of perforations is seen, to be sure that you have not missed an additional perforation.

Clinical findings following both penetrating and blunt trauma to the small intestine may be minimal at first. This is because much of the small bowel content is relatively sterile and has a nearly neutral pH which may produce little inflammatory response. This is not true of injuries to the duodenum where the highly alkaline contents cause an immediate severe peritoneal response. If the duodenal injury is posterior, retroperitoneal signs may be absent. At this hospital where all penetrating wounds of the abdomen are treated by exploration, a perforating wound of the intestine is rarely, if ever, overlooked. The lag between injury and clinical manifestation of a small bowel perforation may be long and may even extend to days if expectant management is utilized.

Small bowel injury following blunt trauma may be difficult to diagnose. It must be considered even if initial signs of intraabdominal injury are absent. This is particularly true of patients who have been wearing seat belts when involved in automobile accidents. There are a number of reports in the literature describing lacerations of the mesentery which result in devascularization of a loop of bowel which did not become manifest clinically until hours or days after an auto accident.

At the time of abdominal exploration there are certain findings which, if present, require exploration of the duodenum:

- Hematoma about the duodenum, the head of the pancreas, the base of the transverse mesocolon, or at the base of the small bowel mesentery.
- Crepitation about the duodenum indicating air in the retroperitoneal tissues.
- Bile discoloration about the duodenum. This may be a dark green color or brown or so dark that true bile staining may not be identifiable.
- Fat necrosis about the duodenum.
- Edema about the duodenum.

Small wounds may be closed with a single layer of seromuscular nonabsorbable sutures. Larger wounds are more of a problem since closure may result in stenosis. If the large wound is below the ampulla of Vater, complete division of the duodenum and anastomosis to the more distal duodenum or to the jejunum may be done. If opposite the ampulla or superior to it, some other method of treatment must be used. One method is to close the wound; carry out antrectomy, vagotomy and gastrojejunostomy, and close the duodenal stump. This has been called "duodenal diverticulization" by Berne and the rationale for the procedure is diversion of gastric contents from the area of duodenal injury so as to avoid activation of pancreatic enzyme. The duodenal wound may be reinforced by a "serosal patch" thus substantially reducing the possibility of a duodenal fistula. Another method of treating a large duodenal wound is by side-to-side gastroduodenostomy using the duodenal defect as the duodenal stoma.

Duodenal injuries should be decompressed either by a nasogastric tube if no resection has been done or by catheter decompression if the wound has been severe enough to require duodenal diverticulization and construction or gastrojejunostomy.

If a duodenal hematoma is seen at the time of early exploration, it should be evacuated. It must be done gently so as to avoid converting an intramural hematoma into a perforating wound of the duodenum. If the patient is seen several days after injury, a duodenal hematoma may be suspected because of bilious vomiting, abdominal and back pain, and on rare occasions testicular pain. The diagnosis is established by the finding of a duodenal obstruction associated with the "coiled spring" sign or "stack of coins" sign in which the prominent mucosal folds show a helical pattern on x-ray contrast studies. Many duodenal hematomas will respond to nasogastric suction. A period of 10 to 12 days of conservative care is indicated. If the hematoma has not subsided by that time, operation and evacuation of the hematoma are indicated.

DR. BLAISDELL: *Dr. Christensen, would you be more specific about the nature of seat belt injuries?*

DR. CHRISTENSEN: Seat belt injuries are usually caused by compression of the bowel or the mesentery or both by the seat belt against the spinal column. Shearing caused by sudden deceleration may tear bowel from its attachments or avulse the mesentery from the bowel. Laboratory investigation has shown that rupture of the bowel occurs rarely due to increase in intraluminal pressure alone. It is probably necessary that the bowel be obstructed at two places so as to produce a closed loop if rupture is to be produced. Injuries to the lumbar spine frequently accompany seat belt injuries to the abdominal organs.

Many seat belt injuries are due to an improperly placed belt. The belt lies across the abdomen rather than across the pelvis, or at the time of the accident the patient slips underneath the belt and the force is applied to the abdomen. A big problem with seat belt injuries is making the diagnosis. Physical findings may be minimal at first, and a number of cases are reported in the literature in which the diagnosis was delayed for several days. One reason for this is that the injury is primarily mesenteric and produces devascularization of a segment of small bowel rather than immediate rupture.

DR. BLAISDELL: *Would you please be specific on at what point in perforating injuries you would elect to resect the bowel? I realize it is a matter of judgment, but do you have a rule of thumb that we could use to work with?*

DR. CHRISTENSEN: When the diameter of the lacerations in a given segment of bowel equals the diameter of the bowel you have a clear indication for resection and anastomosis. If we had to sew up four 1 cm lacerations of the bowel and the circumference of the bowel was 4 cm, that would be clear-cut indication to resect and anastomose. In gunshot wounds in which there is a need to debride, by the time you have completed your debridement you may have a wound large enough to warrant resection and anastomosis. When doing an anastomosis you can see what you are doing, you can get rid of devitalized bowel. If you elect to close large wounds, you may not be able to see what the mucosa looks like and you probably have a greater potential for a breakdown. The only area where I would be conservative would be in the duodenum and the terminal ileum. The ileocecal valve has important anatomical functions and many absorptive functions are found in the distal ileum.

DR. BLAISDELL: *Would you describe the incision you use for exploratory laparotomy?*

DR. CHRISTENSEN: The standard incision is a midline laparotomy incision. We can miss holes if our laparotomy wounds are too small, for, as a consequence, it is difficult to carry out an adequate exploration. Any missed perforation of the small bowel may mean a fatality in an otherwise good-risk, young, healthy patient. It is my opinion that far more complications result from missed perforations than from breakdown of a small bowel closure or anastomosis. The good blood supply of the small intestine combined with low bacterial counts in the lumen result in prompt healing as a general rule.

A PHYSICIAN: *Dr. Christensen, would you describe in more detail how you place sutures for closure of small bowel lacerations and how you carry out small bowel anastomosis?*

DR. CHRISTENSEN: I use a one-layer closure consisting of nonabsorbable sutures. A purse string can be used to close small perforations. For larger wounds I use interrupted seromuscular Lembert sutures. In doing an anastomosis I first cut the bowel back to healthy bleeding mucosa and then apply a Carmalt, Allen or other intestinal clamp obliquely across the bowel ends with the tip of the clamp directed to the mesenteric border. The clamp should be angled so that the bowel when divided will be longer on the mesenteric side than on the antimesenteric side. I then place a seromuscular, nonabsorbable 3-0 or 4-0 suture between the ends of the bowel on the mesenteric border. It is important to have the border cleared of fat. The next suture is placed opposite the first on the antimesenteric borders of the bowel. A row of similar sutures is then placed between the first two sutures completing one suture line. Then with a knife I cut adjacent to the clamps removing the crushed bowel and opening the lumen of the loops. The anastomosis is completed by placing an anterior row of sutures in the same manner as the posterior row was placed.

DR. BLAISDELL: *Dr. Christensen, how do you manage injuries to the mesentery when there is a large mesenteric hematoma? How do you close lacerations of the mesentery?*

Dr. Christensen: Large hematomas of the mesentery should be explored since the superior mesenteric artery or one of its major branches may be involved. Hemorrhage can generally be controlled by pressure. After evacuating the hematoma, small bleeding vessels may be ligated. Injuries to larger arteries should be repaired, if feasible, to avoid ischemia of the bowel, and therefore, bleeding vessels should not be crushed and ligated before they are fully identified. Mesenteric rents should be closed by continuous or interrupted sutures placed with care so as to avoid further injury to blood vessels.

A Physician: *How do you determine viability of the bowel when there has been mesenteric vascular injury? How do you determine how much small intestine to resect?*

Dr. Christensen: If the bowel has a normal appearance and responds to pinching with peristalsis, it is viable. If it is dusky on the outside the mucosa is probably dead or dying and resection is indicated. Hypovolemia causes poor perfusion and it is important to restore blood volume when trying to determine whether or not bowel is viable. Pulsations in the small vessels of the arcades should be felt for and if present indicate that the bowel will probably remain viable even though it may not look healthy when you first see it.

If you have to resect, the resection should be carried back to where the wall of the bowel including the mucosa bleeds. That is why an open anastomosis is optimal.

If mesenteric injury results in extensive resection being necessary, and at the time of closure there is any question about the viability of the remaining bowel, a second look 24 hours later is indicated. This permits removal of any residual peritoneal blood and resection of marginal appearing segments of the bowel back to bleeding mucosa. This permits a maximal amount of bowel to be salvaged with minimal risk to small bowel fistulae.

Dr. Blaisdell: I think we will close the discussion on that last point. Review of our series of gastrointestinal injuries time and again reinforces Dr. Christensen's statement. When there is any doubt about hemostasis or viability of bowel, reoperation within 24 hours is mandatory. Patients tolerate repeated laparotomy well. They do not tolerate bowel disruption or leakage, and these complications are the ones that lead to fatality.

Informed
OPINION

Refer to: Hassard H: Medical injury compensation—An approach to the professional liability problem (Informed Opinion). West J Med 123:503-506, Dec 1975

Medical Injury Compensation

An Approach to the Professional Liability Problem

HOWARD HASSARD, Esq., *San Francisco*
Legal Counsel, California Medical Association

TODAY, THROUGHOUT the United States, personal injuries received by a person outside of employment are that person's problem, and any expenses involved are his burden, unless (1) he is the beneficiary of some type of public or private health benefit or disability income; or (2) he can prove in a court of law that he suffered the injury because of the negligence or willful act of someone else (and, I might add, if the wrongdoing someone else is insured).

If our injured person is lucky, he receives compensation from both sources—that is to say, he carries health insurance and he successfully sues someone else for negligence in causing the injury. Furthermore, the fact that the injury may have actually been proximately caused by someone's negligence does not necessarily mean that he will collect adequate monetary compensation. His lawyer may not present his case very well, a jury may be sympathetic to the tort feasor or the responsible second party (that is, the tort feasor) may be both broke and uninsured—or any number of other events could intervene and deny monetary compensation. Conversely, if our innocent injured person is extremely lucky, he could receive compensation from his catastrophic health insurance policy, and also recover damages in court against a richly insured second party—even though the second party was not, in fact, negligent—if our injured innocent is a superb thespian, or his lawyer is, and a jury can be mesmerized into thinking an award should be made.

Basically, the present legal system applicable to personal injury involves a trial by combat, is adversary in nature and the outcome can—and most often is—influenced by factors that have nothing to do with the injured person's needs or the true causes of the injury.

This legal system has been both attacked and defended. To the Michigan Physicians' Crisis Committee it is a ripoff. To Mr. Robert Cartwright, President of the Association of Trial Lawyers of America, it is the "very cement of our society." Mr. Cartwright says that by bringing medical malpractice suits "the trial lawyer performs a service not only for his individual client, but for the public at large." The legal concept of providing monetary compensation for an injury caused by negligent or other wrongful conduct is called tort law. It is stoutly defended by lawyers who represent the plaintiffs in personal injury litigation as a public service, a deterrent to careless conduct and a significant force in improvement in quality of performance.

Let us examine what the present jury trial tort

This address was presented as part of a general session on The Professional Liability Problem—A Review of Alternatives at the 86th Annual Meeting of the Washington State Medical Association, Seattle, September 19, 1975.

Reprint requests to: Brad Davis, Director, Professional Liability Activities, California Medical Association, 731 Market Street, San Francisco, CA 94103.

system, predicated on fault, really involves as applied to the health care field. Without bogging down in statistics, I think I am able, from long years of experience as an attorney representing medical organizations and physicians individually, to identify "the way it is" and the real impact on patient and physician alike.

To begin with, in the metropolitan areas where most people live, the time interval from injury to final solution is many years in most cases and several years at the very least—and one 1974 California Supreme Court case involved a surgical operation done in 1949. Assuming a patient was injured as a direct consequence of medical carelessness or incompetence, a delay of 5 to 25 years in awarding compensation can be disastrous, and is obviously unfair.

Second, as indicated in my opening remarks, the end result of tort litigation is uneven and unpredictable. The injured patient, as well as the physician sued, are in a roulette game.

Third, an abrasive contest is involved that produces side effects that cannot possibly be considered to be in the public interest. The very legal words that are the cornerstone of tort law—negligence, wrong doing, fault, tort feasor—all sound to a dedicated professional as accusatory of immorality, incompetency, criminality or worse. While these words are commonplace to attorneys and have little significance to the public (when, for instance, an automobile accident is the subject of suit), it is a different ballgame when a person's professional life is on the line—and that is true for lawyers as well as for physicians.

Fourth, the system is not only time-consuming, it is extremely costly. Breakdowns of what happens to each malpractice insurance dollar show that less than 40 percent of each dollar actually goes to the injured patient, and that something close to half the premium dollar is spent in investigating, defending and litigating claims. But this is not the whole story. Taxpayers pay for the court system and medical malpractice trials are lengthy. The man-days of productivity that are lost because of medical liability disputes is incalculable. Add defensive medicine, and we have a total cost that is astronomical.

Fifth, there is a total absence of any public responsibility after a decision has been made to pay X number of dollars to an injured patient. The tort system quits at that point. Nothing is done to assure that the compensation paid will be used for the purpose intended. For all our tort laws care, the money can go down a rathole. Rehabilitation is an unknown word in our tort system. Unless the parties involved voluntarily agree to establish a trust fund, a permanently injured patient has no assurance that a lump sum award will be used for his care. The tort system really stops at the 18th Century insofar as responsibility for the well-being of the injured person is concerned.

A system that is painfully slow to function, and is uneven, abrasive, costly and lacking in any meaningful care for the injured person, seems to me to be archaic and infinitely inferior to the capabilities of the people of today. I cannot believe that the system that I have outlined is the best we can do near the end of the 20th century. Ripoff or not, it does not work, and things are going to get worse.

As has frequently been pointed out, modern medicine and modern health institutions are extremely complex and they are getting more complex every day. People will live longer and be healthier because of modern medicine, but there will be more injuries—whether caused by fault or simply the complexity of things. To toss the social problem of personal injuries incurred during medical care to the current tort system simply is not fair and the obvious breakdown that is occurring will get worse.

I have advocated the development of a new compensation system and regardless of details, I am firmly convinced that a new system is a must. I am perfectly aware that the frequency of medically induced injuries is much greater than the frequency of malpractice claims, and hence I am also aware that those who fear the cost of a new system have a point. But cost or no cost, some mechanism must be found so that injured patients are treated equally and fairly and are compensated promptly and in relationship to the need. It is not cast in concrete that the cost of medical injuries must be borne solely by the providers of care. Spreading the risk among patients as well as the providers can be achieved. The utilization of health insurance, which the overwhelming majority of Americans have, has to be fully explored. These and other means to finance a new compensation system need to be researched in depth.

Another objection that has been loudly voiced to a new compensation system is that, if it is no-fault oriented, definition of a compensible event is extremely difficult and necessarily involves con-

tinuation of the adversary nature of all claimant proceedings. And I must agree that the various proposals for a complete no-fault system that I have studied all have either very complex or somewhat unsatisfactory approaches toward identifying what are injuries and what injuries are compensible. I suspect that the first new compensation system that is tried will involve a modified fault system with emphasis toward determining causation (that is, was the injury actually caused by deviant or erroneous medical intervention?) and determining the need for compensation.

The most sweeping replacement of the common law tort system with a compensation system in the English speaking world was launched in New Zealand early in 1974. Essentially, New Zealand adopted a universal accident compensation plan under which all accident victims, regardless of fault and regardless of where the accident occurred, are compensated for their lost pay and medical expenses, and if necessary are taken care of for the rest of their lives. The New Zealand system, then in its formative stages, was described in detail in an article prepared for the Department of Health, Education, and Welfare's Commission on Medical Malpractice. The article, " 'No Fault' Compensation for Personal Injuries in New Zealand," by Arthur Berstein, was published beginning at page 836 of the Appendix to the Commission Report.[1] The proposed New Zealand system described by Mr. Berstein covers all accidental personal injuries, including those incurred during medical management. The common law tort system, traditional in New Zealand, was jettisoned in favor of a compensation commission. The planners had difficulties with identifying the compensible event in medical management situations, and had difficulties with cost. However, in spite of all of the problems that have been identified with no-fault compensation, New Zealand went ahead.

On September 16, 1975 *The Wall Street Journal* carried a lead article, datelined Wellington, New Zealand, describing the universal accident compensation system as it actually works. Presumably it is working reasonably well. The cost is funded by a tax on wages, plus a share of automobile registration fees. The government pays directly for nonearners, such as housewives and foreign visitors. In the first year, 105,000 claims were presented—New Zealand's population is around 3 million. However, only about $33 million was paid out.

With respect to medical malpractice, *The Wall Street Journal* article states:

> Another perplexity is medical malpractice, which is now complicated because of the prohibition against lawsuits. Obvious cases like leaving something in the wound are covered, but the difficult area is misdiagnosis or failure to follow standard medical practice. The commission has paid out in some cases, but mainly it's feeling its way.

Without doubt, the giant leap from the tort system to a universal accident compensation plan is beyond the real world for this country at this time. Nevertheless, I would urge that those of us who are interested in the medical professional liability problem keep in touch with New Zealand's experience and endeavor to profit by that country's great experiment.

To the best of my knowledge, basic research to date in this country on how to design a compensation system is very meager. Much more needs to be done. One very small study that was done for the Department of Health, Education, and Welfare's Malpractice Commission by Dr. John Boyden, Jr.,[2] seems to me to point the way for meaningful research in this area. Dr. Boyden studied 400 patient records, 100 derived from a teaching hospital and 300 from a hospital having no house staff. He undertook to ascertain injuries resulting from medical management: good, bad or indifferent. Of the 400 cases studied, he found 27 patients who suffered injuries caused, or probably caused, by medical management. Of these, 22 could be classified as minor, and 5 as quite serious. Obviously, this was a small study, and no reliable conclusions can be drawn. Dr. Boyden felt that his pilot study at least indicated that a much larger study should be undertaken. However, this has not been done.

In any new compensation system, the needs of the patient and the welfare of society should be the twin goals. Duplication of compensation should be avoided, needed care and assistance should be prompt, return to a useful role in society (that is, rehabilitation) should be of primary concern and not only should permanently injured patients receive rehabilitation attention but compensation should be geared to need and not be a massive lump sum. Waste and unevenness of awarding compensation should be avoided. Cost must be spread in such a fashion that no one is put out of business or forced to shoulder more

than a fair share, and the consuming public must be involved. Stated simply, in the area of injuries resulting from medical management we ought to utilize the know-how and skills that we have developed and utilized in other areas of personal injury.

May I close with a quotation that intrigues me. It appears in an article that discusses the merits of the jury system and it comments on those that say the public considers jury trial an inviolate fundamental right. This is the quotation:

> The voices that are heard are those that rise above the sound of the axes that their owners are grinding. While these protagonists speak in the name of the community or in the name of God, there is no proof of the delegation of authority to speak for either.[3]

REFERENCES

1. Berstein A: "No-fault" compensation for personal injury in New Zealand, *In* Report of the Secretary's Commission on Medical Malpractice, Appendix, DHEW Publication No. (OS) 73-89. Washington, DC, Department of Health, Education, and Welfare, Jan 16, 1973, pp 836-848
2. Boyden JS Jr: Medical injury in hospital patient records, *In* Secretary's Commission on Medical Malpractice, Appendix, DHEW Publication No. (OS) 73-89. Washington, DC, Department of Health, Education, and Welfare, Jan 16, 1973, pp 41-49
3. Steuer A: The case against the jury (A brief without citations). NY State Bar J 47:101-146, Feb 1975, p 140

The Cure for Obesity

The cure for obesity, of course, has been known for centuries. For example, in 1825 a famous French gourmet said that any cure for obesity must begin with the three following absolute precepts: discretion in eating, moderation in sleeping and exercise on foot and horseback. In other words, one must decrease the intake of energy and increase its expenditure. However, most of the diet programs do not work. The magnitude of our society's concern for quick weight loss is reflected by the sales of two recent diet books: Dr. Stillman's books have sold 5 million copies in the last six years and Dr. Atkins' book sold 1 million copies in the first seven months. However, these books are just a drop in the bucket when viewed in terms of the billions of dollars per year which are pumped into the diet industry. In the end, however, the struggle continues for most people because dieting is very difficult. There is no easy way, no quick way to lose weight.

—HENRY A. JORDAN, MD, *Philadelphia*
Extracted from *Audio-Digest Family Practice*, Vol. 23, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057

CONSULTANTS FOR

The Western Journal of Medicine in 1975

The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to The Journal during the past year.

Adams, John E.
Amend, William
Amini, Fariborz
Anderson, Raymond C.
Ardell, David S.
Asbury, Arthur

Banfield, William
Barbaccia, Joseph C.
Bard, Gregory
Barker, Wiley F.
Barrett-Connor, Elizabeth
Barry, A. L.
Becker, Charles E.
Benfield, John R.
Benson, John A., Jr.
Berk, John E.
Biglieri, Edward G.
Blaisdell, F. William
Blois, M. Scott
Boldrey, Edwin B.
Boles, Roger
Boushey, Homer
Braff, Erwin H.
Brandborg, Lloyd
Brecher, George
Brill, Norman Q.
Brown, Howard A.
Butler, John

Cavalieri, Ralph
Charles, Gerald
Chatterjee, Kanu
Cheitlin, Melvin D.
Clark, Albert G.
Clark, Dan
Cline, Martin J.
Coggs, Granville
Cohen, Peter
Cohen, Richard
Conte, John E., Jr.
Corkill, Guy
Cosentino, Anthony M.
Credé Robert H.
Cudmore, John T. P.
Cullen, Stuart C.
Curreri, P. William
Curry, Francis

Daniels, John R.
Darling, Louise
Davidson, Robert M.
Deal, Ronald
Dedo, Herbert H.
deLorimier, Alfred A.
Dement, William C.
Diamond, Louis K.
Dodge, Harold
Drew, Lawrence
Dunphy, J. Englebert
du Vivier, Anthony

Ehrenfeld, William K.
Einstein, Hans E.
Elliott, Henry W.
Elmendorf, Thomas
Engleman, Ephraim P.
Epstein, Charles J.
Epstein, Wallace

Fairley, H. Barrie
Fish, Barbara
Fitzgerald, Faith
French, James W.
Friedman, Michael
Fries, James
Fye, Kenneth

Gallagher, Donald
Gamsu, Gordon
Gerbode, Frank L.
Goetsch, Carl
Gofman, Helen
Gold, Warren M.
Golde, David W.
Goldman, Mervin J.
Goldman, Michael
Goldsmith, Robert
Goodman, Julien M.
Gray, Gary M.
Greenberg, Robert E.
Greenspan, Francis S.
Greer, Monte A.
Grossman, Moses
Gruberg, Kermit H.
Grumbach, Melvin
Gullion, David
Guze, Lucien B.

Hall, Thomas C.
Hamilton, William K.
Harrison, Donald C.
Hassard, Howard
Haviland, James W.
Hine, Charles H.
Hinman, Frank, Jr.
Hoeprich, Paul
Hoff, Julian T.
Hogan, Michael J.
Hollenberg, Milton
Holman, Halsted
Hopewell, Philip
Hopper, James, Jr.
Humphreys, Michael
Hunt, Thomas K.

Jamison, Rex L.
Jones, Michael
Jones, Reese T.
Julien, Peter J.
Juul, Clement O.

Kaplan, Selna L.
Karliner, Joel S.
Kimura, Samuel J.
Kirby, William M. W.
Knudson, Harlan R.
Korsch, Barbara
Krikes, Nicholas P.
Kurze, Theodore

Lee, Jane F.
Lee, Philip R.
Levine, David G.
Light, Jack
Lucas, Donald B.
Lyon, Richards P.

Macrae, Donald
Maffly, Roy
Margolis, Alan
Margulis, Alexander
Martin, David W., Jr.
Marty, Alan T.
Masouredis, Sam
McCluskey, Robert T.
McElwain, Richard A.
Merigan, Thomas C.
Meyer, Richard
Mills, John
Morris, R. Curtis
Murray, John F.
Murray, William R.

Nadel, Jay A.
Novey, Harold S.
Nye, Dan A.

Ockner, Robert
Odell, William D.
Odujinrin, Oluwole O.
O'Loughlin, Bernard J.
O'Rourke, Robert A.

Pappagianis, Demosthenes
Penny, Robert
Perkins, Herbert A.
Pevehouse, Byron C.
Phillips, Theodore L.
Popp, Richard
Powell, Malcolm R.
Price, David C.

Rapaport, Samuel I.
Raskin, David E.
Resnik, Barbara
Reynolds, Telfer B.
Roe, Robert L.
Rosenbaum, Ernest H.
Rosenberg, Saul A.
Ross, Joseph
Rubsamen, David

Sadler, H. Harrison
Sadusk, Joseph F.
Sahud, Mervyn A.
St. Geme, Joseph W., Jr.
Saunders, David R.
Schaffarzick, Ralph W.
Schambelan, Morris
Schaupp, Willis
Scheinman, Melvin M.
Schiller, Nelson
Schrock, Theodore
Sebastian, Anthony
Selzer, Arthur
Shapiro, Howard A.
Sharma, Om P.
Shaw, Edward B.
Shearn, Martin A.
Sheiner, Lewis
Sheline, Glenn E.
Shumway, Norman E.
Smith, David E.
Smith, Donald R.
Snyder, Leo
Sokolow, Maurice
Solomon, David H.
Spitler, Lynn E.
Spivack, Samuel D.
Starkweather, John A.
Steele, Muriel
Stern, W. Eugene
Stoller, Robert
Stoney, Ronald J.
Sunshine, Philip
Swan, Jeremy

Tennenhouse, Daniel J.
Thaler, M. Michael
Thomas, Ralph
Thompson, James H.
Tooley, William H.
Trunkey, Donald D.
Turkington, Roger W.

Ullyot, Daniel J.

VanderLaan, W. P.
Vandervoort, Herbert E.
Vaughan, Thomas
Veith, Ilza
Vera, Zakauddin
Vyas, Girish

Wagner, Peter
Wallerstein, Ralph O.
Wasserman, Karl
Watts, Harvey David
Way, E. Leong
Way, Lawrence W.
Weinstein, Louis
Weller, Charles
White, Laurens P.
Whiting, William B.
Wiggins, Howell E.
Williams, David E.
Wilson, Charles B.
Wilson, John T., Jr.
Woeber, Kenneth
Wood, David A.
Wylie, Edwin J.

Yatsu, Frank
Yeazell, Jeanette

Zielinski, Florian W.

in memoriam

Allen, Robert Emmet, San Francisco. Died September 13, 1975 in Oakland, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Allen was a retired member of the San Francisco Medical Society.

Bosworth, Howard W., Los Angeles. Died June 26, 1975 of injuries received in automobile accident on Pacific Coast Highway in Malibu, aged 80. Graduate of the University of Buffalo School of Medicine, 1921. Licensed in California in 1925. Dr. Bosworth was a member of the Los Angeles County Medical Association.

Bussey, Donald George, Long Beach. Died September 22, 1975 in Rochester, Minnesota, aged 76. Graduate of State University of Iowa College of Medicine, Iowa City, 1924. Licensed in California in 1927. Dr. Bussey was a member of the Los Angeles County Medical Association.

Epstein, Norman, San Francisco. Died October 5, 1975 in Finland, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Dr. Epstein was a member of the San Francisco Medical Society.

Freeman, Robert G., Pasadena. Died September 6, 1975 in Pasadena of heart disease, aged 65. Graduate of McGill University Faculty of Medicine, Montreal, 1936. Licensed in California in 1937. Dr. Freeman was a member of the Los Angeles County Medical Association.

Gratiot, John H., Monterey. Died September 24, 1975 in Monterey of pulmonary embolism, aged 68. Graduate of Harvard Medical School, Boston, 1932. Licensed in California in 1935. Dr. Gratiot was a member of the Monterey County Medical Society.

Hambo, Curtis Clifford, Carmichael. Died in September 1975, aged 69. Graduate of the University of Oregon Medical School, Portland, 1932. Licensed in California in 1933. Dr. Hambo was a retired member of the Sacramento County Medical Association.

Harmon, Robert J. P., Richmond. Died October 7, 1975 in Richmond of cerebral thrombosis, aged 87. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1914. Licensed in California in 1921. Dr. Harmon was a retired member of the Alameda-Contra Costa Medical Association.

Inglizian, Artin A., Los Angeles. Died April 5, 1975 in Los Angeles of heart disease, aged 65. Graduate of American University of Beirut School of Medicine, 1935. Licensed in California in 1952. Dr. Inglizian was a member of the Los Angeles County Medical Association.

Kohn, Martin Malcolm, Burlingame. Died September 19, 1975 in Burlingame, aged 56. Graduate of the University of Chicago, the School of Medicine, 1950. Licensed in California in 1953. Dr. Kohn was a member of the San Mateo County Medical Society.

Lawrence, Fred H., San Francisco. Died June 25, 1975 of heart disease, aged 65. Graduate of the University of Illinois School of Medicine, Chicago, 1937. Licensed in California in 1937. Dr. Lawrence was a member of the San Francisco Medical Society.

Leigh, Morton Digby, Los Angeles. Died September 5, 1975 in Palm Springs of cancer, aged 70. Graduate of McGill University Faculty of Medicine, Montreal, 1932. Licensed in California in 1954. Dr. Leigh was a retired member of the Los Angeles County Medical Association.

Linstrum, John Wesley, Marysville. Died October 1, 1975 in Marysville, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1935. Licensed in California in 1935. Dr. Linstrum was a member of the Yuba-Sutter-Colusa County Medical Society.

Mueller, Esther, Encino. Died August 16, 1975 in Los Angeles of hemorrhage from bleeding ulcer, aged 48. Graduate of Hadassah Medical School, Hebrew University, Jerusalem, 1956. Licensed in California in 1968. Dr. Mueller was a member of the Los Angeles County Medical Association.

Paap, George F., Long Beach. Died September 20, 1975 in Lake Arrowhead of heart disease, aged 74. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1931. Dr. Paap was a member of the Los Angeles County Medical Association.

Paddie, Louis Kliege, Santa Monica. Died August 29, 1975 in Battle Creek, Michigan of heart disease, aged 68. Graduate of the University of Arkansas School of Medicine, Little Rock, 1940. Licensed in California in 1946. Dr. Paddie was a member of the Los Angeles County Medical Association.

Webster, Charles Matthew, Sacramento. Died September 22, 1975, aged 61. Graduate of Northwestern University Medical School, Chicago, 1941. Licensed in California in 1941. Dr. Webster was a member of the Sacramento County Medical Association.

Weyman, Arnold E., Northridge. Died September 22, 1975 of heart disease, aged 59. Graduate of Philadelphia College of Osteopathy, 1946. Licensed in California in 1947. MD degree from California College of Medicine, 1962. Dr. Weyman was a member of the Los Angeles County Medical Association.

Wissner, Ulrich C., Los Angeles. Died September 12, 1975 in Loma Linda of heart disease, aged 64. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1941. Licensed in California in 1941. Dr. Wissner was a member of the Los Angeles County Medical Association.

AUTHOR INDEX

Abbasi, Abdul S., Los Angeles 228
Anderson, Hjalmar, Los Angeles 350
Anderson, Rose Ann, San Francisco 63
Arnold, Hubert A., Davis, CA 147
Ayers, Larry N., Oklahoma City 255

Barrett, Peter V. D., Torrance, CA 204
Barrett-Connor, Elizabeth, La Jolla 22
Bauer, Julius, Beverly Hills 316
Bayer, Arnold S., Torrance, CA 404
Benfield, John R., Torrance, CA 396
Bennett, William M., Portland 372
Blaisdell, F. William,
San Francisco 64, 148, 236, 321, 499
Block, Alvin L., Napa 154
Blumberg, Bruce D., San Francisco 188
Boushey, Homer, San Francisco 31
Bradshaw, Christy L., La Jolla 17
Brater, D. Craig, San Francisco 393
Braun, Judith, San Diego 115
Bray, George A., Torrance, CA 396
Brenner, R. James, Torrance, CA 404
Brown, Josiah, Los Angeles 441
Burns, R. Stanley, San Francisco 345
Butler, Leona M., San Francisco 328

Caldwell, James H., Seattle 58
Campbell, Robert A., Portland 1
Carmalt, Janice E., Davis, CA 311
Caro, Xavier J., San Francisco 41
Charney, Philip, South Lake Tahoe 62
Chaterjee, Satya N., Los Angeles 184
Christensen, Norman, San Francisco 499
Cole, Harold S., Los Angeles 441
Combs, Darrel T., San Francisco 407
Cooper, John A. D., Washington, DC 225
Cooperman, Lawrence R., Redwood City, CA 360
Corrado, Robbie, San Francisco 345
Crowder, John E., Orange, CA 247
Curreri, P. William, Seattle 275

Deftos, Leonard J., La Jolla 447
de Groot, Walter P. H., Seattle 61
DeLong, W. Bradford, San Francisco 92
Dement, William C., Stanford 7
DeQuattro, Vincent, Los Angeles 441
Dixson, Barbara K., San Diego 17

Earle, John, Stanford 340
Eddy, John R., Stanford 325
Eldridge, Frederic L., Stanford 7
Engle, Robert B., Laguna Beach, CA 61
Ensinck, John W., Seattle 76

Fein, Jerry, Torrance, CA 255
Fiala, Milan, Torrance, CA 202
Fitzgerald, Faith, San Francisco 490
Foran, Robert F., Los Angeles 269, 431

Gak, Carl, Oakland 496
Galpin, Jeffrey E., Torrance, CA 404
Gardner, Jerry D., Bethesda 309
Gilliland, Bruce C., Seattle 58
Ginsberg, Marvin L., Torrance, CA 255
Glauser, Frederick L., Long Beach 492
Glazener, Frederic S., San Francisco 41
Gleason, Ray E., Boston 319
Golbus, Mitchell S., San Francisco 188
Gold, Warren M., San Francisco 49
Goldman, Mervin J., San Francisco 467
Goldstein, Elliot, Davis, CA 311
Goldstein, Gideon, New York City 138
Greenberg, Richard N., New Orleans 497
Greenfield, Sheldon, Los Angeles 350
Greenwood, Ronald D., Boston 239
Gross, Stephen R., La Jolla, CA 194
Guidotti, Tee L., La Jolla, CA 69
Guilleminault, Christian, Stanford 7
Guze, Lucien B., Los Angeles 48, 404

Hamburger, Bette, San Francisco 250
Handmaker, Hirsch, San Francisco 63
Harner, Marvin H., Portland 1
Harwood, Ivan, San Diego 282
Hassard, Howard, San Francisco 503
Hawes, Warren E., Berkeley 81
Hine, Charles H., San Francisco 101
Correction 324
Hirschman, Shalom Z., New York City 224
Holmes, King K., Seattle 367
Howard, Matthew L., Ukiah 147
Howell, R. Rodney, Houston 223
Hultgren, Herbert N., Palo Alto 407
Humphreys, Michael H., San Francisco 148
Hunt, Thomas K., San Francisco 305

Jacobson, Lester B., San Francisco 314
James, Stuart H., Johnson City, New York 345
Jawetz, Ernest, San Francisco 87
Jimerson, David, San Diego 115
Jones, Michael W., San Francisco 250
Jones, Oliver W., La Jolla 17

Kent, Deryck R., Irvine 145
Klaeveman, Hayden, San Francisco 290
Knapp, William, Davis, CA 399
Knoernschild, Harvey E., San Jose 318
Komaroff, Anthony L., Boston 350
Krone, Lawrence R., La Jolla 17
Kunkel, Frederick W., San Francisco 51

Lawson, Russell K., Portland 1
Layzer, Robert B., San Francisco 123
Lerner, Steven E., San Francisco 345
Levin, Phillip M., Los Angeles 269, 431
Lewis, Jerry P., Davis, CA 399
Lim, Robert C., San Francisco 321
Long, Howard F., Pleasanton, CA 145
Lowitz, Barry B., Sepulveda, CA 60
Luckey, Marjorie, San Francisco 490

Marvin, Janet A., Seattle 275
Meares, Edwin M., Jr., Boston 436
Merliss, R. R., Beverly Hills 418
Mikuriya, Tod H., Berkeley 62
Miller, Richard R., Davis, CA 399
Mischler, Elaine, San Diego 282
Mitchell, Dace B., San Francisco 41
Mohler, John G., Los Angeles 159
Morgan, Annabelle, Los Angeles 350
Morrelli, Howard F., San Francisco 393
Morrison, James, San Diego 115
Moutsopoulos, Haralampos M., San Francisco 496
Musgrave, James E., Portland 1

Neumann, Kurt, San Francisco 51

Nissen, Edward D., Irvine 145
Nyhan, William L., San Diego 282
Oberman, Arthur E., Los Angeles 184
Olmsted, Nancy, San Diego 282
Pardee, Geraldine P., Seattle 76
Parker, Robert G., Seattle 337
Parthemore, Jacqueline G., La Jolla 447
Pasi, Aurelio, San Francisco 101
Petersdorf, Robert G., Seattle 135
Peterson, Raymond M., San Diego 17
Pfeifer, James F., Palo Alto 407
Pheasant, Homer C., Los Angeles 317
Piel, Carolyn F., San Francisco 486
Prichard, Lorraine L., La Jolla 17
Rabens, Richard, San Diego 282
Raskin, Neil H., San Francisco 211
Reimer, George W., Redwood, City, CA 360
Reiss, Eric, Miami, Florida 488
Reza, Michael J., Los Angeles 228, 441
Richardson, R. Garratt, Seattle 337
Robb, Leon G., Los Angeles 231
Roos, Bernard A., La Jolla 447
Rose, Augustus S., Los Angeles 316
Rossiter, Stanford B., Redwood City, CA 360
Sachs, David D., San Francisco 395
Santos, Perry, Ventura 417
Sawada, Shigewasa, San Francisco 496
Scheinman, Melvin M., San Francisco 51
Schlachter, Max, Oakland 146
Schnoll, Sidney H., Philadelphia 345
Schofferman, Jerome, Torrance, CA 160
Schrock, Theodore R., San Francisco 236
Schultz, Amelia L., Seattle 76
Seltzer, Ronald A., Redwood City, CA 360
Shaub, Michael, Los Angeles 265
Shearn, Martin A., Oakland 496
Sheldon, George F., San Francisco 64, 148
Shettigar, U. R., Palo Alto 407
Shore, Ernest H., Los Angeles 269, 431
Simmon, F. Blair, Stanford 7
Simon, Roger P., San Francisco 164
Siperstein, Marvin D., San Francisco 319
Smith, William Richard, Irvine 492
Spiro, Robert G., Boston 319
St. Geme, Joseph W., Jr., Torrance, CA 306
Stone, Richard A., San Diego 108
Stubblebine, J. M., Greenbrae 240
Sulzberger, Marion B., San Francisco 417
Sutherland, Paul W., San Francisco 141
Talwalkar, Yeshawent B., Portland 1
Theis, Jerold, Davis, CA 311
Thomas, David Vernon, Los Altos 317
Thorpe, James H., Sacramento 418
Treiman, Richard L., Los Angeles 269, 431
Tretheway, D. G., San Diego 53
Tri, Terry B., San Francisco 407
Trunkey, Donald D.,
San Francisco 64, 148, 236, 321, 499
U, Hoi Sang, San Francisco 175
Van Herle, Andre J., Los Angeles 441
Vieweg, W. V. R., San Diego 53
Von Hoff, Daniel D., San Francisco 490
Wallace, Jeanne, San Francisco 490
Walsh, John H., Torrance, CA 206
Wasserman, Karlman, Torrance, CA 255
Weaver, James E., Cincinnati 145
Weinstein, Eugene C., Van Nuys 56
Weller, Michael, San Diego 282
Wilson, Charles B., San Francisco 175
Wilson, Robert, Los Angeles 265
Winickoff, Richard N., Boston 350
Wiseman, L. Ward, Anaheim 71
Yamauchi, Terry, Torrance, CA 160
Yoshikawa, Thomas T., Torrance, CA 202
Young, Roy T., Los Angeles 441
Zacherle, Barry, San Francisco 380

IN MEMORIAM

Adler, Ethel, May 3, 1975 85
Allen, Robert Emmet, Sep 13, 1975 508
Anderson, Carsten Russell, Aug 12, 1975 423
Anderson, William Thayer, May 11, 1975 85
Babington, Suren H., May 8, 1975 85
Baker, Charles P., Jun 11, 1975 342
Balius, Edward Francis, May 26, 1975 173
Beigelman, Maurice N., Jun 20, 1975 342
Bell, John C., Apr 28, 1975 173
Correction 342
Benzinger, Martin, Apr 19, 1975 85
Bishop, Katherine Scott, Sep 20, 1975 423
Blong, Peter H., Jun 7, 1975 173
Boehm, Marie Lenore, Jun 30, 1975 342
Boelter, Muriel Daphne Diana, Aug 15, 1975 ... 342
Bosworth, Howard W., Jun 26, 1975 508
Bovill, Grace M. Talbott, Aug 26, 1975 344
Bussey, Donald George, Sep 22, 1975 508
Christensen, Valdemar E., Mar 16, 1975 85
Coleman, LeGrand L., Jul 4, 1975 342
Coman, Charles P., Apr 29, 1975 85
Crabtree, Hodge N., May 26, 1975 173
Dahle, Ben Maurice, Jul 13, 1975 342
Daitch, Maurice L., May 27, 1975 342
Dakin, Wirt Bradley, May 24, 1975 342
Diamant, Bernard, Jun 27, 1975 342
Durgin, Rubie Mae, May 26, 1975 85
Dwiggins, Jack Harlan, May 23, 1975 342
Dwyer, William Francis, May 30, 1975 173
Eagleston, Frederick LeRoy, Aug 8, 1975 423
Edwards, Charles Frederick, Mar 2, 1975 85
Epstein, Norman, Oct 5, 1975 508
Felsen, Louis, Jun 17, 1975 342
Fishbein, A. Allan, Aug 19, 1975 342
Fishman, Sidney A., Jun 3, 1975 342
Fitzgibbon, Joseph Paul, Mar 12, 1975 173
Flynn, George W., Jun 2, 1975 173
Fogle, Jimmy L., Jun 22, 1975 342
Frame, Paul W., Jr., Jul 18, 1975 342
Francoeur, Jules André, Aug 3, 1975 423
Frantz, Kieffer E., May 11, 1975 342
Freeman, Norman E., Aug 9, 1975 343
Freeman, Robert G., Sep 6, 1975 508
Frey, Russell Gregory, Apr 2, 1975 85
Gamette, Douglas Leon, Aug 12, 1975 343
Gerstle, Mark L., Aug 1, 1975 343
Glascock, Fred Leib, Jul 9, 1975 343
Glick, Louis Joseph, Sep 16, 1975 423
Gratiot, John H., Sep 24, 1975 508
Griffiths, Robert Owen, Jun 19, 1975 173
Guardino, Salvator J., Aug 6, 1975 343
Guldseth, Gustav Daniel, Jan 18, 1975 343

Hambo, Curtis Clifford, Sep 1975 508
Harmon, Robert J. P., Oct 7, 1975 508
Harris, Harold Isadore, May 3, 1975 85
Haschka, August J., May 6, 1975 173
Hawes, Ralph E., Jan 1, 1975 173
Harris, Trester Smith, Sep 21, 1975 423
Hayden, Ralph Orville, Jan 6, 1975 173
Helming, Oscar C., Jr., Jun 8, 1975 173
Herrman, Albert J., Apr 10, 1975 173
Hershey, Peter, Jun 12, 1975 343
Herzikoff, Sam Sidney, Mar 30, 1975 85
Hidey, Robert M., May 12, 1975 173
Hoffman, Philip B., Apr 22, 1975 85
Holland, Frank F., Mar 19, 1975 85
Horwitz, Moris, May 30, 1975 343
Hoyer, E. Charles, Jun 24, 1975 343
Hurwitz, Ethel Adler, May 3, 1975 85
Inglizian, Artin A., Apr 5, 1975 508
Jacobs, John Theodore, Jr., Aug 9, 1975 343
Jones, J. Roy, May 30, 1975 85
Katibah, Edmund M., Sep 11, 1975 423
Kelley, Harry Warner, Aug 12, 1975 343
Kidwell, Thomas Thurman, Apr 23, 1975 85
Kilfoy, Edward Joseph, May 12, 1975 85
Kohn, Martin Malcolm, Sep 19, 1975 508
Kottke, Elmer E., Dec 2, 1974 85
Kully, Barney M., Apr 16, 1975 86
Lawrence, Fred H., Jun 25, 1975 508
Leary, William G., Jun 15, 1975 173
Leidig, Lawrence R., May 10, 1975 423
Leigh, Morton Digby, Sep 5, 1975 508
Levin, Grant, Sep 23, 1975 423
Levin, Marcia J., Sep 25, 1975 423
Lichty, John M., May 4, 1975 86
Linstrom, John Wesley, Oct 1, 1975 508
Livingston, Afton Munk, May 23, 1975 173
Lones, Frank Elwin, Sep 14, 1975 423
Lovely, James Phillip, Sr., May 6, 1975 86
Lum, Donald D., Sep 16, 1975 423
MacColl, Douglas R., Apr 23, 1975 173
Magid, George Joseph, Apr 27, 1975 86
Marasco, Fred Bernard, Jul 2, 1975 343
Marubayashi, Stanley T., Aug 15, 1975 343
Maxwell, Ralph Earl, Jul 18, 1975 343
McClure, James Clifton, Jun 15, 1975 343
McGuinness, Joseph Stanley, May 22, 1975 86
McKinne, Rubie Mae Durgin, May 26, 1975 85
Michelson, Lewis, Jul 5, 1975 343
Mueller, Esther, Aug 16, 1975 508
Nelson, Albert E., May 4, 1975 174
Newel, Clarence D., May 30, 1975 343
O'Farrell, Norman Morris, Apr 6, 1975 86
Ogden, Roderick A., Sep 11, 1975 423
Ohanneson, John, Jun 27, 1975 343
Paap, George F., Sep 20, 1975 508
Paddie, Louis Kliege, Aug 29, 1975 508
Pennington, Alma Stevens, Feb 19, 1975 343
Powers, Harry James, Apr 3, 1975 86
Putnam, Tracy J., Mar 29, 1975 86
Quarry, Paul Thomas, Apr 7, 1975 86
Reeves, William Rollin, Jan 3, 1975 174
Reithmayer, Edwin N., Apr 24, 1975 86
Sanderson, George H., Jun 3, 1975 174
Schweifler, John, Aug 4, 1975 343
Settle, Francis Boas, Feb 26, 1975 86
Sherrick, John Wesley, Jun 20, 1975 174
Shubin, Stanley Herbert, Jun 29, 1975 344
Smith, Lawrence Willis, Mar 21, 1975 174
Smith, Steward H., Jan 31, 1975 344
Smithies, Harold Riddiough, Jul 27, 1975 344
Sweeney, John Paul, May 26, 1975 344
Talbott, Grace M. Bovill, Aug 26, 1975 344
Telford, Percy K., Jul 2, 1975 423
Terry, Charles Taylor, Jul 28, 1975 423
Thebaut, William Maxwell, Jr., Jul 8, 1975 344
Thompson, Harold Lincoln, Aug 28, 1975 423
Tornell, Robert R., Apr 24, 1975 423
Tyler, Edward T., Jul 30, 1975 423
Ulrich, George John, Jul 8, 1975 344
Van Sicklin, Roy, Jul 16, 1975 344
Waligora, Daniel John, Dec 5, 1974 344
Wallace, William Earl, Aug 24, 1975 423
Wanless, John F., Jun 19, 1975 344
Waters, Wayne Walter, May 4, 1975 86
Watson, James Lowell, Jun 22, 1975 343
Webster, Charles Matthew, Sep 22, 1975 508
Weyman, Arnold E., Sep 22, 1975 508
Wissner, Ulrich C., Sep 12, 1975 508
Wolfe, Nathalie M., Aug 16, 1975 343
Wong, Arnold Vardoc, Jun 1975 344
Zarowitz, Daniel G., May 24, 1975 174

SUBJECT INDEX

A

Abdominal Aortic Aneurysms, see *Ruptured*
Abdominal Vascular Injuries (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Robert C. Lim 321
Abortion, see *Psychological Sequelae*
Acute Eosinophilic Leukemia Associated with Neutropenia, Richard R. Miller, Jerry P. Lewis, William Knapp 399
Acute Renal Failure in Trauma Patients (Trauma Rounds), Chief Discussants: Michael H. Humphreys, George Sheldon 148
Addiction, see *Anxiety Neurosis*
Adenomatosis Type II (Sipple's Syndrome), see *Multiple Endocrine*
Adrenergic Function in Hypertensive Patients, see *Dopamine-Beta-Hydroxylase*
Advances in the Clinical Care of Burned Patients (Medical Progress), P. William Curreri, Janet A. Marvin 275
Editorial, Thomas K. Hunt 305
Advances in Clinical Medicine, see *Epitomes*
Advice to Travelers (Medical Progress), Elizabeth Barrett-Connor 22
Editorial, Lucien B. Guze 48
[Allograft Survival], see *Pediatric Renal Transplantation*
[Anesthesiologists, Withholding of Services], see *Malpractice Insurance*
Aneurysms, see *Ruptured Abdominal*
Aneurysms, Intracranial, see *Diagnostic Pitfalls*
Animal Models of Glycogen Storage Conditions—Their Relation to Human Disease (Medical Progress), Stephen R. Gross 194
Editorial, R. Rodney Howell 223
Antimicrobial Drugs, see *Combination*
Antimicrobial Drugs, see *Synergism and Antagonism*
Antenatal Diagnosis of an XXX Female—A Dilemma for Genetic Counseling, Lawrence R. Krone, Lorraine L. Prichard, Christy L. Brad-

shaw, Oliver W. Jones, Raymond M. Peterson, Barbara K. Dixson 17
Anxiety Neurosis, Depressive Disorder and Meprobamate Addiction (UC, San Diego, and San Diego VA Hospital) (Psychiatric Rounds), Case Presentation: Judith Braun; Patient Interview: James Morrison; Discussants: David Jimerson, James Morrison 115
Aortic Aneurysms, see *Ruptured Abdominal*
Aortic Regurgitation, see *Demand Pacemaker*
Apnea Syndrome, see *Sleep*
Are Research Subjects Really Informed? (Informed Consent), Amelia L. Schultz, Geraldine P. Pardee, John W. Ensinck 76
Arthritis, see *Severe Disabling Poly-*
[Arthritis, Septic], see *Splash in the Joint*
Atrial Tachycardia, see *Demand Pacemaker*

B

Back Pain, see *Nurse-Protocol Management*
Bacterial Endocarditis, see *Severe Disabling Polyarthritis*
Blood Gases: Believe It or Not (Clinical Note), John G. Mohler 159

Book Reviews:

Abdominal Operations—6th Ed., Vol. 1 & 2, *Maingot et al* 254
Advances in Primary Care *Kallstrom & Yarnall (Page End)* 498
Beneficent Euthanasia, *Kohl* 424
Courage to Fail, *Fox & Swazey* 425
Current Pediatric Diagnosis & Treatment—3rd Ed., *Kempe et al* 254
Diagnostic and Therapeutic Aids in Urology, *Bodner et al* 254
Effects of Hospitalization on Children, The, *Oremland & Oremland* 427
Fitness, Health, and Work Capacity, *Larson* 426
Handbook of Psychiatry—3rd Ed., *Solomon & Patch* 428
Heroin Addiction in Britain, *Judson* 427
Immunological Aspects of Skin Diseases, *Fry & Seah* 430
Lupus Erythematosus—2nd Ed., *Dubois* 429
Major Problems in Dermatology—Vol 2, see *Microbiology of Human Skin*
Microbiology of Human Skin—Vol 2 in the Series: Major Problems in Dermatology, *Noble & Somerville* 424
Microorganisms and Human Disease, *Meyer* 426
Principles of Drug Action: The Basis of Pharmacology—2nd Ed., *Goldstein et al* 429

Bovine Heterografts for Hemodialysis, Robert F. Foran, Ernest H. Shore, Phillip M. Levin, Richard L. Treiman 269
Breast, see *Diagnosis of Carcinoma*
Breast Cancer, see *Xeromammography*

Bureau of Research and Planning:

Physician Supply in California (December 1973)—Socioeconomic Report of the Bureau of Research and Planning, CMA, Michael W. Jones, Bette Hamburger 250
Letter to Editor, R. R. Merliss 418

Burned Patients, see *Advances in the Clinical Care of*

C

Calcium and Skeletal Metabolism (Medical Progress), Leonard J, Deftos, Bernard A. Roos, Jacqueline G. Parthemore 447
Editorial, Eric Reiss 488
Calcium Metabolism (Editorial), Eric Reiss 488

California Medical Association:

Annual Session Program, follows page 430
Committee on Evolving Trends in Society Affecting Life, and Advisory Panels on Obstetrics and Gynecology, Pathology, and Psychiatry, Guidelines for the Interview and Examination of Alleged Rape Victims 420
Guidelines for the Interview and Examination of Alleged Rape Victims, see *Committee on Evolving Trends in Society*
Physician Supply in California (December 1973)—Socioeconomic Report, Bureau of Research and Planning (Information), Michael W. Jones, Bette Hamburger 250
Letter to Editor, R. R. Merliss 418
Proposed Constitutional Amendments for Action in 1976, see Annual Session Program (page 16)
Thyroid Cancer—Delayed Effects of Head and Neck Irradiation in Children (Medical Information), John Earle (CMA Advisory Panel on Radiology) 340

Cancer, see *Thyroid*
Cancer, Breast, see *Xeromammography*
Cancer, Primary, see *Metastases*
Cancer Immunotherapy: A Word of Caution About "A Word of Cautious Dissent" (Letter to Editor), Barry B. Lowitz 60
Candide Becomes a Doctor (From a Medical Student), John R. Eddy 325
Carcinoma, Breast, see *Diagnosis of*
Cardiomyopathy, see *Congestive*
Chest Diseases, Advances in, see *Epitomes*
Cholera, see *Pancreatic*
[Cholera Vaccination Requirements], see *Advice to Travelers*
Clinical and Pathological Findings and Sequelae of Viral Hepatitis, Peter V. D. Barrett, see *Viral Hepatitis*
Clinical Care of Burned Patients (Editorial), Thomas K. Hunt 305
Clinical Medicine, Advances, see *Epitomes*

Clinical Note:

Blood Gases: Believe It or Not, John G. Mohler .. 159

Colon, see *Injuries of*
Combination Antimicrobial Drugs (Editorial), Robert G. Petersdorf 135
Complications in Renal Transplant Recipients, see *Ocular*
Community Hospital Experience, see *Xeromammography*
Community Hospitals, see *Continuing Medical Education*
Compensation, see *Medical Injury*
Conga Drumming, see *Traumatic Hemoglobinuria*
Congestive Cardiomyopathy in Hypothyroidism, Michael J. Reza, Abdul S. Abbasi 228
Conscience of the Physician, see *Motivation*
Consciousness, Loss of, see *Syncope and*
Continuing Medical Education, see *Third Segment*
Continuing Medical Education in Community Hospitals (Editorial) 140

Continuing Medical Education in Smaller Hospitals (Letter to Editor), James H. Thorpe 418
Continuing Medical Education in the Small Community Hospital (Medical Education), Alvin L. Block 154
Editorial 140
Letter to Editor, James H. Thorpe 418
Contraceptives, Oral [Liver Tumors with], see *Registry for*
Coronary Arteriograms, see *Transmural Myocardial Infarction*
Correction, see *Manganese Intoxication*
Counseling, Genetic, see *Antenatal Diagnosis*
Croup and Epiglottitis (UC, San Diego, Interdepartmental Conference), Participants: Ivan Harwood, Nancy Olmsted, Richard Rabens, Elaine Mischler, Michael Weller, William L. Nyhan 282
Editorial, Joseph W. St. Geme, Jr. 306
Cysticercosis, see *Spinal*
Cysts, Benign, see *Diagnosis of Carcinoma*

D

Demand Pacemaker for Refractory Atrial Tachycardia in a Patient with Aortic Regurgitation, U. R. Shettigar, James F. Pfeifer, Herbert N. Hultgren 407
Demand Pacing, see *T Wave Sensing*
Depressive Disorder, see *Anxiety Neurosis*
Dermatitis, see *Soap Photo-*
Detection of Gonorrhea, see *Screening and the*
Diabetic Microangiopathy (Letter to Editor), Robert G. Spiro, Ray E. Gleason 319
Author Replies, Marvin D. Siperstein 319
Diagnosis of Carcinoma and Benign Cysts of the Breast (Letter to Editor), Robert B. Engle 61
Reply, Walter P. J. de Groot 61
Diagnostic Pitfalls of Subarachnoid Hemorrhage from Intracranial Aneurysms, W. Bradford DeLong 92
Diarrheal Syndromes, see *Pancreatic*
Diffusing Capacity, Specific Diffusing Capacity and Interpretation of Diffusion Defects, Larry N. Ayers, Marvin L. Ginsberg, Jerry Fein, Karlman Wasserman 255
Dopamine-Beta-Hydroxylase—An Index of Adrenergic Function in Hypertensive Patients (Medical Progress), Richard A. Stone 108
[Drug Abuse], see *Phencyclidine*
[Drug] Addiction, see *Anxiety Neurosis*
Drug Combinations in Topical Therapy (Letter to Editor), Marion B. Sulzberger 417
[Drug] Induced Interstitial Nephritis, see *Methicillin*
Drug Therapy, see *Rational*
Drug Therapy in Patients with Renal Disease, see *Principles of*
Drugs, see *Combination Antimicrobial*
[Drugs], see *Overdose*
Drugs, see *Synergism and Antagonism*
Drumming, Conga, see *Traumatic Hemoglobinuria*
Duodenum, see *Injuries to*

E

Editorials (General and Scientific):

General:

Continuing Medical Education in Community Hospitals 140
Federal Support for Medical Schools, John A. D. Cooper 225
First Decade of Federal Medicine 307
Forward Plan for Health for the Years 1977-1981 . 485
Job Action by Physicians, A [Malpractice Crisis . . . Withholding Services] 305
Malpractice and Social Change 47
Malpractice Insurance—Can the Private Sector Do It? 394
Medical Information for Travelers, Lucien B. Guze 48
Motivation and Conscience of the Physician 48
On Withholding of Physicians' Services 136
Letter to Editor, Homer C. Pheasant 317
Routine Screening of Asymptomatic Women for Gonorrhea, David D. Sachs 395
Third Segment of Medical Education, The 222
Will Private Medicine Self-Destruct? 489

Scientific:

Calcium Metabolism, Eric Reiss 488
Clinical Care of Burned Patients, Thomas K. Hunt 305
Combination Antimicrobial Drugs, Robert G. Petersdorf 135
Croup and Epiglottitis, Joseph W. St. Geme, Jr. ... 306
Hemolytic Uremic Syndrome, Carolyn F. Piel 486
Is Obesity a Surgical Disease?, John R. Benfield, George A. Bray 396
Man, Mice and Glycogen Storage, R. Rodney Howell 223
Medical Information for Travelers, Lucien B. Guze 48
"Myasthenia Gravis"—Or the Autoimmunity, Thymic Disease, Neuromuscular Block Poser, Gideon Goldstein 138
Pancreatic Cholera, Jerry D. Gardner 309
Promising Developments in Viral Hepatitis, Shalom Z. Hirschman 224
Pulmonary Vascular Disease, Warren M. Gold ... 49
Rational Drug Therapy in Patients with Renal Disease, D. Craig Brater, Howard F. Morrelli .. 393
Routine Screening of Asymptomatic Women for Gonorrhea, David D. Sachs 395

Education, see *Financing*
Endocarditis, Bacterial, see *Severe Disabling Polyarthritis*
[Environmental Health], see *Manganese Intoxication*
Epiglottitis, see *Croup and*

Epitomes:

Chest Diseases 41
Neurology 128
Otolaryngology 218
General and Family Practice 297
Nuclear Medicine 386
Pathology 477

Ergot, see *Severe Vasospasm Following*

F

Family Practice, Advances in, see *Epitomes*
Far-Advanced Pulmonary Interstitial Disease [from Paraquat Poisoning] with Normal Findings on a Chest Radiograph, Frederick L. Glauser, William Richard Smith 492
Federal Medicine, see *First Decade*
Federal Support for Medical Schools (Editorial), John A. D. Cooper 225
Female, XXX, see *Antenatal Diagnosis*

Financing Undergraduate Medical Education (Medical Education), John E. Crowder 247
Editorial, John A. D. Cooper 225
First Decade of Federal Medicine (Editorial) 307
Fluoridation (Letters to the Editor), Max Schlachter, Matthew L. Howard, Hubert A. Arnold 146
Forward Plan for Health for the Years 1977-1981 (Editorial) 485
Fothergill's Neuralgia [Tic Douloureux, Trigeminal Neuralgia] (Historical Note Page End), Richard D. Greenwood 239

From a Medical Student:

Medicine, Critical Science, and the Real World, Tee L. Guidotti 69
Candide Becomes a Doctor, John R. Eddy 325

G

Gases, see *Blood*
[Gastroenteritis, Infectious], see *Travelers' Diarrhea and Others*
General and Family Practice, Advances in, see *Epitomes*
Genetic Counseling, see *Antenatal Diagnosis*
Glycogen Storage, see *Animal Models*
Glycogen Storage, see *Man, Mice*
[Gonococcal Urethritis], see *Infectious Urethritis*
Gonorrhea, see *Routine Screening*
Gonorrhea, see *Screening and the Detection of*
Grange [Malpractice Insurance], see *Medical*
Guidelines for the Interview and Examination of Alleged Rape Victims, CMA Committee on the Evolving Trends in Society Affecting Life; and the Advisory Panels on Obstetrics and Gynecology, Pathology, and Psychiatry of the CMA Scientific Board 420
"Gurney" Again—Scots Origin Theory Scotched? (Letter to Editor), David Vernon Thomas 317
Gynecology, Advisory Panel, see *Guidelines for Interview and Examination of Alleged Rape*

H

Harbor General Hospital, see *Specialty Conferences*
[Headache], see *Migraine*
Head and Neck Irradiation, see *Thyroid Cancer*
Health, see *Forward Plan*
Health Professions Student Scholarship Program, A (Letter to the Editor), Perry Santos 417
[Heart Disease], see *Transmural Myocardial Infarction*
Hemodialysis, see *Bovine Heterografts for*
Hemodynamic Changes, see *Sleep Apnea*
Hemoglobinuria, see *Traumatic*
Hemolytic-Uremic Syndrome (UC, San Diego, and University Hospital of San Diego, Pediatric Grand Rounds), Participants: Stanley A. Mendoza, Guillermo Mendoza 459
Editorial, Carolyn F. Piel 486
Hepatitis, see *Promising Developments*
Hepatitis, see *Viral*
Herpes Progenitalis, see *Herpes Type 2*
Herpes Type 2 Meningitis Following Herpes Progenitalis, Daniel D. Von Hoff, Marjorie Luckey, Jeanne Wallace, Faith Fitzgerald 490
Heterografts, see *Bovine Heterografts for*
[High School] Student Scholarship, see *Health Professions*

Historical Note:

Fothergill's Neuralgia [Tic Douloureux, Trigeminal Neuralgia], Ronald D. Greenwood 238

Hospital, see *Continuing Medical Education in the Small Community*
Hypertensive Patients, see *Dopamine-Beta-Hydroxylase—An Index of Adrenergic Function in*
Hypothyroidism, see *Congestive Cardiomyopathy*

I

[Immunization], see *Advice to Travelers*
Immunotherapy, see *Cancer*
[Infectious Diseases], see *Advice to Travelers*
Infectious Urethritis in Men and Women—Diagnosis and Treatment, Edwin M. Meares, Jr. 436

Information:

(See also *Medical Information*)
Guidelines for the Interview and Examination of Alleged Rape Victims, CMA Committee on the Evolving Trends in Society Affecting Life; and the CMA Advisory Panels to the Scientific Board on Obstetrics and Gynecology, Pathology, and Psychiatry 420
Physician Supply in California (December 1973) Socioeconomic Report of the CMA Bureau of Research and Planning, Michael W. Jones, Bette Hamburger 250
Letter to Editor, R. R. Merliss 418

[Informed Consent], see *On Informing the Patient*

Informed Consent:

Are Research Subjects Really Informed?, Amelia L. Schultz, Geraldine P. Pardee, John W. Ensinck .. 76

Informed Opinion:

Medical Injury Compensation—An Approach to the Professional Liability Problem, Howard Hassard 503
Recommendations for Some Medi-Cal Improvement, J. M. Stubblebine 240

Informing the Patient, see *On*
Injuries of the Colon and Rectum (Trauma Rounds), Chief Discussant: Theodore R. Schrock 236
Injuries to Duodenum, Small Intestine and Mesentery (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Norman Christensen 499
Intensive Care Centers in California, Newborn, see *Survey of*
Interstitial Disease [Due to Paraquat Poisoning], see *Far-Advanced*
Interstitial Nephritis, see *Methicillin Induced*
Intestine, Small, see *Injuries to Duodenum*
Intoxication and Fatalities, see *Phencyclidine*
Intracranial Vascular Malformations, see *Surgical Treatment of*
Irradiation in Children, see *Thyroid Cancer*
Is Obesity a Surgical Disease? (Editorial), John R. Benfield, George A. Bray 396

J

Job Action by Physicians, A [Malpractice Crisis . . . Withholding of Services, Presbyterian Medical Center] (Editorial) 305
Joint, see *Splash in the*

K

Knuckle Cracking, see *Surreptitious*

L

Laetrile, see *More on*

Letters to Editor:

Cancer Immunotherapy: A Word of Caution About "A Word of Cautious Dissent," Barry B. Lowitz . 60
Continuing Medical Education in Smaller Hospitals, James H. Thorpe 418
Diabetic Microangiopathy, Robert G. Spiro, Ray E. Gleason 319
Reply, Marvin D. Siperstein 319
Diagnosis of Carcinoma and Benign Cysts of the Breast, Robert B. Engle 61
Reply, Walter P. H. de Groot 61
Drug Combinations in Topical Therapy, Marion B. Sulzberger 417
Fluoridation, Max Schlachter, Matthew L. Howard, Hubert A. Arnold 146
"Gurney" Again—Scots Origin Theory Scotched?, David Vernon Thomas 317
Health Professions Student Scholarship Program, A, Perry Santos 417
"Medical Grange" for Malpractice Insurance, A, Harvey E. Knoernschild 318
More on Laetrile, Tod H. Mikuriya 62
NPR's (Non-Physician Representatives) for Medicare, Howard F. Long 145
On Informing the Patient, Augustus S. Rose 316
Physician Supply in California, R. R. Merliss 418
Registry for Liver Tumors Associated with Oral Contraceptives, Edward D. Nissen, Deryck R. Kent 145
Renal Imaging and Pyelonephritis, Hirsch Handmaker, Rose Ann Anderson 63
Sjögren's Syndrome with Light Chain Myeloma, Martin A. Shearn, Haralampos M. Moutsopoulos, Shigewasa Sawada, Carl Gak 496
Sleep Apnea, Julius Bauer 316
Soap Photodermatitis, James E. Weaver 145
Surreptitious Knuckle Cracking, Philip Charney .. 62
Travelers' Diarrhea and Others, Richard N. Greenberg 497
Withholding of Physicians' Services, Homer C. Pheasant 317

Leukemia Associated with Neutropenia, see *Acute Eosinophilic*
Liver Tumors, see *Registry*
Loss of Consciousness, see *Syncope*
Low Back Pain, see *Nurse-Protocol Management*

M

[Malaria], see *Advice to Travelers*
[Malpractice], see *Res Ipsa Loquitur*
[Malpractice], see *Will Private Medicine Self-Destruct?*
Malpractice and Social Change (Editorial) 47
[Malpractice Crisis], see *Job Action by Physicians*
[Malpractice Crisis], see *On Withholding of Physicians' Services*
Malpractice Insurance, see *"Medical Grange"*
[Malpractice Insurance], see *Medical Injury*
[Malpractice Insurance], see *Withholding of Physicians' Services*
Malpractice Insurance—A Crisis in Medicine [Withholding of Physicians' Services, Pacific Medical Center], Leona M. Butler 328
Editorial: Job Action by Physicians 305
Malpractice Insurance—Can the Private Sector Do It? (Editorial) 394
Man, Mice and Glycogen Storage (Editorial), R. Rodney Howell 223
Manganese Intoxication, Charles H. Hine, Aurelio Pasi 101
Correction 324
Maternal and Child Care Health Programs (Page End) 264
Medi-Cal, see *Recommendations*

Medical Education:

Continuing Medical Education in the Small Community Hospital, Alvin L. Block 154
Editorial 140
Letter to Editor, James H. Thorpe 418
Financing Undergraduate Medical Education, John E. Crowder 247
Editorial, John A. D. Cooper 225

Medical Education, see *Third Segment*
Medical Education in the Small Community Hospital, see *Continuing Medical*
"Medical Grange" for Malpractice Insurance, A (Letter to Editor), Harvey E. Knoernschild 318

Medical Information:

Metastases from Undetected Primary Cancers—Clinical Experience at a Radiation Oncology Center, R. Garratt Richardson, Robert G. Parker .. 337
Overdose—The Early Treatment, Jerome Schofferman, Terry Yamauchi 160
Syncope and Transient Loss of Consciousness—Differential Diagnosis and Treatment, Roger P. Simon 164
Thyroid Cancer—Delayed Effects of Head and Neck Irradiation in Children, John Earle 340

Medical Information for Travelers (Editorial), Lucien B. Guze 48
Medical Injury Compensation—An Approach to the Professional Liability Problem (Informed Opinion), Howard Hassard 503
[Medical Malpractice], see *Res Ipsa Loquitur*
Medical Schools, see *Federal Support*

Medical Staff Conferences:

Pulmonary Vascular Disease, Chief Discussant: Homer Boushey 31
Editorial, Warren M. Gold 49
Myasthenia Gravis and the Thymus Gland, Chief Discussant: Robert B. Layzer 123
Editorial, Gideon Goldstein 138
Migraine, Chief Discussant: Neil H. Raskin 211
Pancreatic Diarrheal Syndromes, Chief Discussant: Hayden Klaeveman 290
Editorial, Jerry D. Gardner 309
Methicillin Induced Interstitial Nephritis, Chief Discussant: Barry Zacherle 380
Pericarditis, Chief Discussant: Mervin J. Goldman 467

Medical Progress:

Advice to Travelers, Elizabeth Barrett-Connor 22
Editorial, Lucien B. Guze 48
Dopamine-Beta-Hydroxylase—An Index of Adrenergic Function in Hypertensive Patients, Richard A. Stone 108
Animal Models of Glycogen Storage Conditions—Their Relation to Human Disease, Stephen R. Gross 194
Editorial, R. Rodney Howell 223

Advances in the Clinical Care of Burned Patients, P. William Curreri, Janet A. Marvin 275
Editorial, Thomas K. Hunt 305
Principles of Drug Therapy in Patients with Renal Disease, William M. Bennett 372
Editorial, D. Craig Brater, Howard F. Morrelli . 393
Calcium and Skeletal Metabolism, Leonard J. Deftos, Bernard A. Roos, Jacqueline G. Parthemore 447
Editorial, Eric Reiss 488

[Medical Research], see *Are Research Subjects Really Informed?*
Medical Student, see *From a*
Medicare, see *NPR's for*
Medicine, see *First Decade of Federal*
Medicine, Advances in Clinical, see *Epitomes*
Medicine, Critical Science and the Real World [Research], Tee L. Guidotti 69
Meningitis Following Herpes Progenitalis, see *Herpes Type 2*
Meprobamate Addiction, see *Anxiety Neurosis*
Mesentery, see *Injuries to Duodenum*
Metabolism, see *Calcium*
Metastases from Undetected Primary Cancers—Clinical Experience at a Radiation Oncology Center (Medical Information), R. Garratt Richardson, Robert G. Parker 337
Methicillin Induced Interstitial Nephritis (Medical Staff Conference) 380
Microangiopathy, see *Diabetic*
Migraine (Medical Staff Conference) 211
Mondor's Disease, Eugene C. Weinstein 56
More on Laetrile (Letter to Editor), Tod H. Mikuriya 62
Motivation and Conscience of the Physician (Editorial) 48
Multiple Endocrine Adenomatosis Type II (Sipple's Syndrome) in Twins, Michael J. Reza, Roy T. Young, Andre J. Van Herle, Vincent DeQuattro, Harold S. Cole, Josiah Brown 441
"Myasthenia Gravis"—Or the Autoimmunity, Thymic Disease, Neuromuscular Block Poser (Editorial), Gideon Goldstein 138
Myasthenia Gravis and the Thymus Gland (Medical Staff Conference) 123
Editorial, Gideon Goldstein 138
Myeloma, see *Sjögren's Syndrome*
Myocardial Infarction, see *Transmural*

N

Neck Irradiation, see *Thyroid Cancer*
Nephritis, see *Methicillin Induced Interstitial*
Neurology, Advances in, see *Epitomes*
Neutropenia, see *Acute Eosinophilic Leukemia*
Newborn Intensive Care Centers in California, see *Survey of*
Nodules, Thyroid, see *Ultrasonic Evaluation*
Non-Physician Representatives, see *NPR's for Medicare*
NPR's (Non-Physician Representatives) for Medicare (Letter to Editor), Howard F. Long 145
Nuclear Medicine, Advances in, see *Epitomes*
Nurse-Protocol Management of Low Back Pain—Outcomes, Patient Satisfaction and Efficiency of Primary Care, Sheldon Greenfield, Hjalmar Anderson, Richard N. Winickoff, Annabelle Morgan, Anthony L. Komaroff 350

O

Obesity, see *Is . . . a Surgical Disease?*
Obstetrics, Advisory Panel, see *Guidelines for Interview and Examination of Alleged Rape*
Ocular Complications in Renal Transplant Recipients, Arthur E. Oberman, Satya N. Chatterjee .. 184
On Informing the Patient (Letter to Editor), Augustus S. Rose 316
On Withholding of Physicians' Services [Malpractice Crisis] (Editorial) 136
Letter to Editor, Homer C. Pheasant 317
Oncology Center, see *Metastases*
Oral Contraceptives [Liver Tumors with], see *Registry for*
Oregon Medical Association Annual Session Program 172
Otolaryngology, Important Advances in, see *Epitomes*
[Overdose], see *Phencyclidine*
Overdose—The Early Treatment (Medical Information), Jerome Schofferman, Terry Yamauchi ... 160

P

Pacemaker, see *Demand*
Pacemaker, see *Runaway*
[Pacemaker], see *T Wave Sensing*
[Pacific Medical Center], see *Malpractice Insurance*

Page Ends:

Book Review: Advances in Primary Care, Karlstrom & Yarnall 498
Correction: Manganese Intoxication 324
Fothergill's Neuralgia [Tic Douloureux, Trigeminal Neuralgia] (Historical Note), Ronald D. Greenwood 239
Maternal and Child Care Health Programs 264
VD Placard 366

Pancreatic Cholera (Editorial), Jerry D. Gardner . 309
Pancreatic Diarrheal Syndromes (Medical Staff Conference 290
Editorial, Jerry D. Gardner 309
[Paraquat Poisoning], see *Far Advanced Pulmonary . . . Disease*
Pathology, Advances in, see *Epitomes*
Pathology, Advisory Panel, see *Guidelines for Interview and Examination of Alleged Rape*
Patient, see *On Informing the*
[PCP], see *Phencyclidine*
Pediatric Renal Transplantation, Yeshawant B. Talwalkar, Marvin H. Harner, J. E. Musgrave, R. K. Lawson, R. A. Campbell 1
Pericarditis (Medical Staff Conference) 467
Phencyclidine [PCP]—States of Acute Intoxication and Fatalities, R. Stanley Burns, Steven E. Lerner, Robbie Corrado, Stuart H. James, Sidney H. Schnoll 345
Phenothiazine Induced Ventricular Tachycardia, Terry B. Tri, Darrell T. Combs 412
[Phlebitis], see *Mondor's Disease*
Photodermatitis, see *Soap*
Physician Supply in California (December 1973)—Socioeconomic Report, Bureau of Research and Planning, Michael W. Jones, Bette Hamburger (Information) 250
Letter to Editor, R. R. Merliss 418
Physicians' Services, see *Withholding of*
Primary Cancers, see *Metastases*
[Presbyterian Hospital], see *Malpractice Insurance*

Principles of Drug Therapy in Patients with Renal Disease, William M. Bennett (Medical Progress) 372
Editorial, D. Craig Brater, Howard F. Morrelli .. 393
Professional Liability, see *Medical Injury*

Professional Liability:

Res Ipsa Loquitur, L. Ward Wiseman 71

Progenitalis, Herpes, see *Herpes Type 2 Meningitis*
Promising Developments in Viral Hepatitis (Editorial), Shalom Z. Hirschman 224

Psychiatric Rounds:

Anxiety Neurosis, Depressive Disorder and Meprobamate Addiction (UC, San Diego, and San Diego VA Hospital), Case Presentation: Judith Braun; Patient Interview: James Morrison; Discussants: David Jimerson, James Morrison 115

Psychiatry, Advisory Panel, see *Guidelines for Interview and Examination of Alleged Rape*
Psychological Sequelae of Elective Abortion, Bruce D. Blumberg, Mitchell S. Golbus 188
[Pulmonary Disease], see *Diffusing Capacity . . . and Interpretation of Diffusion Defects*
Pulmonary Interstitial Disease [Due to Paraquat Poisoning], see *Far-Advanced*
Pulmonary Vascular Disease (Medical Staff Conference) 87
Editorial, Warren M. Gold 49
Pyelonephritis, see *Renal Imaging and*

R

Radiation Oncology Center, see *Metastases*
Rape Victims, see *Guidelines for Interview and Examination*
Rational Drug Therapy in Patients with Renal Disease (Editorial), D. Craig Brater, Howard F. Morrelli 393
Recommendations for Some Medi-Cal Improvement (Informed Opinion), J. M. Stubblebine 240
Rectum, see *Injuries of the Colon*
Registry for Liver Tumors Associated with Oral Contraceptives (Letter to Editor), Edward D. Nissen, Deryck R. Kent 145
Renal Disease, see *Principles of Drug Therapy*
Renal Disease, see *Rational Drug Therapy*
Renal Failure, see *Acute*
Renal Imaging and Pyelonephritis (Letter to Editor), Hirsch Handmaker, Rose Ann Anderson 63
Renal Transplant Recipients, see *Ocular Complications*
Renal Transplantation, see *Pediatric*
Res Ipsa Loquitur [Medical Malpractice] L. Ward Wiseman 71
[Research], see *Medicine, Critical Science*
Research Subjects, Really Informed? see *Are*
[Respiratory Diseases], see *Diffusing Capacity . . . and Interpretation of Diffusion Defects*
[Rheumatic Disease], see *Splash in the Joint*
Routine Screening of Asymptomatic Women for Gonorrhea (Editorial), David D. Sachs 395
Runaway Pacemaker—A Serious and Unresolved Problem, Frederick W. Kunkel, Kurt Neumann, Melvin M. Scheinman 51
Ruptured Abdominal Aortic Aneurysms—Surgical Treatment, Phillip M. Levin, Ernest H. Shore, Richard L. Treiman, Robert F. Foran 431

S

San Diego Veterans Administration Hospital, see *Specialty Conferences*
San Francisco General Hospital, see *Trauma Rounds*
Schools, Medical, see *Federal Support*
Science, Critical, and the Real World, see *Medicine,*
Screening and the Detection of Gonorrhea, King K. Holmes 367
Editorial, David D. Sachs 395
Sequelae of Abortion, see *Psychological*
Serology and Epidemiology, John H. Walsh, see *Viral Hepatitis*
Severe Disabling Polyarthritis Associated with Bacterial Endocarditis, Arnold S. Bayer, R. James Brenner, Jeffrey E. Galpin, Lucien B. Guze 404
Severe Vasospasm Following Ergot Administration, Leon G. Robb 231
Sipple's Syndrome, see *Multiple Endocrine Adenomatosis*
Sjögren's Syndrome with Light Chain Myeloma (Letter to Editor), Martin A. Shearn, Haralampos M. Moutsopoulos, Shigewasa Sawada, Carl Gak . 496
Skeletal Metabolism, see *Calcium*
Sleep Apnea (Letter to Editor), Julius Bauer 316
Sleep Apnea Syndrome—Can It Induce Hemodynamic Changes? Christian Guilleminault, Frederic L. Eldridge, F. Blair Simmon, William C. Dement 7
Letter to Editor, Julius Bauer 316
[Smallpox Vaccination], see *Advice to Travelers*
Soap Photodermatitis (Letter to Editor), James E. Weaver 145

Special Articles:

Survey of Newborn Intensive Care Centers in California, Warren E. Hawes 81
Malpractice Insurance—A Crisis in Medicine [Withholding of Physicians' Services, Pacific Medical Center], Leona M. Butler 328
Editorial: Job Action by Physicians 305

Specialty Conferences:

Anxiety Neurosis (UC, San Diego, San Diego VA Hospital) (see *Psychiatric Rounds*) 115
Viral Hepatitis (UC, Los Angeles, and Harbor General Hospital Teaching Conference in Infectious Disease), Moderator: Thomas T. Yoshikawa ... 202
Viral Etiologies of Hepatitis, Milan Fiala 202
Clinical and Pathological Findings and Sequelae of Viral Hepatitis, Peter V. D. Barrett 204
Serology and Epidemiology, John H. Walsh ... 206
Editorial, Shalom Z. Hirschman 224
Croup and Epiglottitis (UC, San Diego, Interdepartmental Conference), Participants: Ivan Harwood, Nancy Olmsted, Richard Rabens, Elaine Mischler, Michael Weller, William L. Nyhan 282
Editorial, Joseph W. St. Geme, Jr. 306
Hemolytic-Uremic Syndrome (UC, San Diego, and University Hospital, San Diego, Pediatric Grand Rounds), Participants: Stanley A. Mendoza, Guillermo Mendoza 459
Editorial, Carolyn F. Piel 486

Spinal Cysticercosis, Janice E. Carmalt, Jerold Theis, Elliot Goldstein 311
Splash in the Joint, A, Bruce C. Gilliland, James H. Caldwell 58
[Strikes by Physicians], see *Will Private Medicine Self-Destruct?*

Student Scholarship, see *Health Professions*
Subarachnoid Hemorrhage, see *Diagnostic Pitfalls of*
Surgical Disease, see *Is Obesity a*
Surgical Treatment of Intracranial Vascular Malformations, Hoi Sang U, Charles B. Wilson 175
Surreptitious Knuckle Cracking (Letter to Editor), Philip Charney 62
Survey of Newborn Intensive Care Centers in California, A, Warren E. Hawes 81
Syncope and Transient Loss of Consciousness—Differential Diagnosis and Treatment (Medical Information), Roger P. Simon 164
Syndrome, see *Hemolytic-Uremic*
Synergism and Antagonism Among Antimicrobial Drugs—A Personal Perspective, Ernest Jawetz .. 87
Editorial, Robert G. Petersdorf 135

T

T Wave Sensing During Temporary Demand Pacing, Lester B. Jacobson 314
Tachycardia, see *Phenothiazine Induced*
[Taenia solium, Misdiagnosed], see *Spinal Cysticercosis*
[Tapeworm, Misdiagnosed], see *Spinal Cysticercosis*
Third Segment of Medical Education, The (Editorial) 222
[Thoracoepigastric Veins, Thrombophlebitis of], see *Mondor's Disease*
[Thrombophlebitis of the Thoracoepigastric Veins], see *Mondor's Disease*
Thymus Gland, see *Myasthenia Gravis and the*
Thyroid Cancer—Delayed Effects of Head and Neck Irradiation in Children (Medical Information), John Earle 340
Thyroid Nodules, see *Ultrasonic Evaluation*
Tic Douloureux, see *Fothergill's Neuralgia*
Topical Therapy, see *Drug Combinations in*
Transfusion Practices in Trauma Patients (Trauma Rounds—San Francisco General Hospital), Chief Discussant: George F. Sheldon 64
Transmural Myocardial Infarction in a Young Man with Normal Coronary Arteriograms, W. V. R. Vieweg, D. G. Tretheway 53
Transplant Recipients, Renal, see *Ocular Complications*
Transplantation, see *Pediatric Renal*
Trauma Patients, see *Acute Renal*
Trauma Patients, see *Transfusion Practices in*

Trauma Rounds:

Transfusion Practices in Trauma Patients, Chief Discussant: George F. Sheldon 64
Acute Renal Failure in Trauma Patients, Chief Discussants: Michael H. Humphreys, George F. Sheldon 148
Injuries of the Colon and Rectum, Chief Discussant: Theodore R. Schrock 236
Abdominal Vascular Injuries, Chief Discussant: Robert C. Lim 321
Injuries to Duodenum, Small Intestine and Mesentery, Chief Discussant: Norman Christensen 499

Traumatic Hemoglobinuria Associated with Conga Drumming, Xavier J. Caro, Paul W. Sutherland, Dace B. Mitchell, Frederic S. Glazener 141
Travelers, see *Advice to*
Travelers, see *Medical Information for*
[Travelers' Diarrhea], see *Advice to Travelers*
Travelers' Diarrhea and Others (Letter to Editor), Richard N. Greenberg 497
Trigeminal Neuralgia, see *Fothergill's*
["Turista"], see *Travelers' Diarrhea*
Twins, see *Multiple Endocrine Adenomatosis Type II (Sipple's Syndrome) in*

U

UC, Los Angeles, see *Specialty Conferences*
UC, San Diego, see *Psychiatric Rounds*
UC, San Diego, see *Specialty Conferences*
UC, San Francisco, see *Medical Staff Conferences*
UC, San Francisco, see *Trauma Rounds*
Ultrasonic Evaluation of Nonfunctioning Thyroid Nodules, The, Michael Shaub, Robert Wilson .. 265
University Hospital, San Diego, see *Specialty Conferences*
[University of Washington], see *Are Research Subjects Really Informed?*
Uremic Syndrome, see *Hemolytic*
[Urethritis, Bacterial], see *Infectious*
[Urethritis, Non-specific], see *Infectious*
Urethritis in Men and Women, see *Infectious*

V

[Vaccination], see *Advice to Travelers*
Vascular Disease, see *Pulmonary*
Vascular Injuries, see *Abdominal*
Vascular Malformations, see *Surgical Treatment of Intracranial*
Vasospasm, see *Severe*
[Venereal Disease], see *Screening and the Detection of Gonorrhea*
Ventricular Tachycardia, see *Phenothiazine Induced*
Viral Etiologies of Hepatitis, Milan Fiala, see *Viral Hepatitis*
Viral Hepatitis (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: Thomas T. Yoshikawa (Specialty Conference) .. 202
Viral Etiologies of Hepatitis, Milan Fiala 202
Clinical and Pathological Findings and Sequelae of Viral Hepatitis, Peter V. D. Barrett 204
Serology and Epidemiology, John H. Walsh 206
Editorial, Shalom Z. Hirschman 224
Viral Hepatitis, see *Promising Developments*

W

Washington State Medical Association Annual Meeting Program 171
[Washington, University of], see *Are Research Subjects Really Informed?*
Will Private Medicine Self-Destruct? (Editorial) .. 489
[Withholding of Physicians Services], see *Malpractice Crisis*
Withholding of Physicians' Services (Letter to Editor), Homer C. Pheasant 317

X

XXX Female, see *Antenatal Diagnosis*
Xeromammography in the Early Detection of Breast Cancer—Community Hospital Experience and Approach, Lawrence R. Cooperman, Ronald A. Seltzer, George W. Reimer, Stanford B. Rossiter 360

Y

[Yellow Fever], see *Advice to Travelers*

(Continued from Page 20)

PHYSICIANS WANTED

STEINBECK COUNTRY: PROGRESSIVE rural group practice located in the Salinas Valley has an immediate need for a RADIOLOGIST and a FAMILY PRACTITIONER. The group, consisting of 10 full-time physicians and 11 consultants representing a wide spectrum of specialties provides medical services on a fee-for-service basis to a population area of approximately 22,000. Included in this area of responsibility is a 40-bed acute care community supported hospital with 6 skilled nursing beds, and a 25-bed intermediate care facility. Top fringe benefits, including competitive starting salary with early affiliation. Please call or send C.V. to: Duane F. Hyde, MD; Southern Monterey County Medical Group (A Professional Corporation), 210 Canal St., King City, CA 93930. (408) 385-5471.

PRACTICE IN BEAUTIFUL SANTA BARBARA. Excellent opportunity for experienced G.P., solo family practice established thirteen years, bilingual (English and Spanish), grossing $120,000 available without cost to qualified physician. Fully equipped office for lease or sale, office staff available, will introduce, available now. Leaving for service Jan. 1976. Night and week coverage shared by eight other physicians. Excellent hospital facilities. Contact D. John Barker, MD, 10 W. Micheltorena St., Santa Barbara, CA 93101—Phone (805) 963-3454.

INTERNISTS, OB-GYNS, PEDIATRICIANS—Openings for Board certified or eligible Internists, OB-Gyns and Pediatricians with established and rapidly growing group practice in the Pomona Valley area. Liberal salary and other benefits including malpractice insurance and medical association dues paid by employer. If interested, please contact: Family Health Medical Group, Keith V. Pearson, Phone: (714) 623-0641.

NEWBURY PARK (THOUSAND OAKS)—VENTURA COUNTY: Pediatrician needed in community of 20,000 population; 100,000 surrounding. Only medical bldg. and only doctors in area include OB-GYN group, dental group and optometrist. Beautiful area with numerous educational and recreational facilities. Fabulous opportunity. Contact: Dr. Bruce Berger or Dr. Rodney Resnik, 2904 Theresa Dr., Newbury Park, CA 91320. Phone: (805) 498-6631.

NEWBURY PARK (THOUSAND OAKS)—VENTURA COUNTY: Internist needed in community of 20,000 population; 100,000 surrounding. Only medical bldg. and only doctors in area include OB-GYN group, dental group and optometrist. Beautiful area with numerous educational and recreational facilities. Fabulous opportunity. Contact: Dr. Bruce Berger or Dr. Rodney Resnik, 2904 Theresa Dr., Newbury Park, CA 91320. Phone: (805) 498-6631.

NEWBURY PARK (THOUSAND OAKS)—VENTURA COUNTY: Family or general practitioner needed in community of 20,000 population; 100,000 surrounding. Only medical bldg. and only doctors in area include OB-GYN group, dental group and optometrist. Beautiful area with numerous educational and recreational facilities. Fabulous opportunity. Contact: Dr. Bruce Berger or Dr. Rodney Resnik, 2904 Theresa Dr., Newbury Park, CA 91320. Phone: (805) 498-6631.

NEED IMMEDIATELY. New innovative community health center has an opening for a family physician. Wide range of clinical, public, mental and rural health activities. Unique opportunity to become involved in a total health care program. California license necessary. Contract range $37,000-$40,950. Contact Trevor D. Glenn, MD, Director of Health, 515 South Cedar Ave., Fresno, CA 93702 or call (209) 488-3743.

ORTHOPEDIC SURGEONS — Thriving teaching hospital adding to Orthopedics Staff. Excellent academic environment. Both reconstructive and trauma orthopedics. Geographic full-time position. Favorable remuneration plan. Professional liability insurance paid. Delightful city. Near national parks. Equal Opportunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center, 445 So. Cedar Ave., Fresno, CA 93702.

PHYSICIANS WANTED

ORTHOPEDIC SURGEON and UROLOGIST, Board Certified, needed at Livermore Veterans Hospital. Ideal living and good climate. Salary dependent on experience and qualifications. Contact: Byron V. Whitney, MD, Chief of Surgical Service, Livermore VA Hospital, Livermore, CA 94550, Telephone (415) 447-2560, Ext. 213.

SITUATIONS WANTED

WOULD LIKE FULL TIME POSITION DOING ORTHOPEDIC OUTPATIENTS. Over 20 years experience. Prior general practice. California born and licensed. Stanford graduate. Write Box 9455. Journal of Western Medicine, 731 Market St., San Francisco, CA 94103.

MEDICAL MICROBIOLOGIST, PH D—Board eligible. Experienced all phases of clinical microbiology, including positions as director and chief. Applied researcher with publications. Have taught graduate and medical students. Desire academic and/or clinical position. West Coast or Hawaii. Available mid-1976. Box No. 9454, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN'S ASSISTANT

PHYSICIANS ASSISTANT, interested in primary care position, available for immediate employment. Contact Martin Solov, 2283 37th Ave., San Francisco, CA 94116; (415) 661-7945.

PRACTICE AVAILABLE

F.P., internal medicine, San Francisco peninsula, 30 years same location, $82,000 gross, $58,000 net, retiring Dec. 1975, will turn over practice free of charge, office fully equipped, hospital 1 mile, rent $500/month, 1,600 sq. ft., suitable for 2 physicians. Write Box 9428, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPAEDIC PRACTICE available by January 1, 1976 for fair market value of six rooms fully equipped office including Westinghouse 200 M.A. x-ray and Kodak X-O-Mat processor. Three hospitals in vicinity. Write or call Z. C. Koenig, MD, 73-970 El Paseo, Palm Desert, CA 92260 (714) 346-3888.

EQUIPPED OFFICES FOR SALE

2 RADIOLOGY OFFICES FOR SALE, equipped for general diagnostic radiology. One suburban, one in San Francisco. Together, grossed $95,000 last year. Established, going practices. (415) 781-6863.

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

MEDICAL SUITE AVAILABLE, NOVEMBER 1, 1975, in the Foothill Medical Building, 21297 Foothill Blvd., Hayward, CA 94541. It consists of 850 sq. ft., 3 treatment rooms, waiting room, nurses station and private doctor's office. The building has an x-ray and medical laboratory, and a pharmacy. It is currently occupied by Family Practice Physicians predominantly. For information call (415) 582-6942.

OFFICE FOR RENT TO—FAMILY PHYSICIAN OR INTERNIST: Twenty-seven-year-old practice offered with rental of fully equipped office in beautiful colonial type bldg; Berkeley, one block from University. Retiring. (415) 524-8372.

BUILDING FOR SALE

FOR SALE—Professional Building—7,000 sq. ft. on approximately one acre prime Eugene location. Excellent opportunity for owner-occupant or investor. P.O. Box 10835, Eugene, Oregon 97401 or (503) 342-4593.

EXPERIENCED CALIFORNIA LICENSED Lab Technician and microbiologist—wishes to set up and/or run basic practical medical laboratory in medical building. **Warren F. Hillman, MT,** 2801 N. Bristol, No. 5, Santa Ana, CA 92706. (714) 543-4695.

LOS ANGELES COUNTY HARBOR GENERAL HOSPITAL

UCLA AFFILIATED MEDICAL CENTER is accepting applications for Residency training in our outstanding Psychiatric program. Training in all aspects of psychiatry including child psychiatry (fully accredited child fellowship program), emergency psychiatry, community psychiatry, psychosomatic medicine, inpatient and outpatient psychiatry. Applicants must be eligible for Calif. Licensure. Salary range: $1,376 per month to $1,836 per month plus fringe benefits. Apply to:

Charles V. Ford, M.D., Director
Psychiatric Residency Training Program
Harbor General Hospital
1000 W. Carson St., Torrance, CA 90509

ASSOCIATE DEAN FOR NEW PRIMARY CARE ORIENTED, MEDICAL EDUCATION PROGRAM CENTERED IN FRESNO, CALIFORNIA

The Associate Dean will administer V.A.-funded educational program with professional and educational responsibilities to the Veterans Administration Hospital, Valley Medical Center, and other clinical facilities and associated community hospitals in the central San Joaquin Valley. Close liaison will also be maintained with the San Francisco campus. Applicants should have an MD degree and demonstrated ability in initiating major new medical education activities based on multi-institution support. The University of California is an Affirmative Action Employer.

Contact: **FRESNO SEARCH COMMITTEE, DEAN'S OFFICE, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, SAN FRANCISCO, CALIFORNIA 94143.**

Excellent opportunity to practice in Ontario, California, a town of 80,000 located midway between Los Angeles and Palm Springs. Hospital draws from an area of over 250,000.

Seeking a **Chief of Pediatrics** (there is no other pediatrician in town), a **Chief of Urology,** a **Chief of Internal Medicine,** and a **Chief of Family Practice.** Free office rent—for six months. Guaranteed $50,000 gross first year. An opportunity to practice a high standard of medicine devoid of any economic stress or competition.

Phone "collect" at **(714) 984-2201**
Chairman, Search Committee

Wanted—

Chief of Pediatrics
Family Practice and Urology

For Ontario Community Hospital, Ontario, California, located midway between Palm Springs and Los Angeles—Population 80,000. No competition. Free office rent for six months. Guaranteed income first year. **Write or phone (714) 984-2201,** Chairman, Search Committee.

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: For a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education, please write to the above address.

CANCER

January 16-17—**Childhood Cancer: Major Clinical Advances and New Problems in Family Adjustment.** Children's Hospital of L.A. and American Cancer Society at Children's Hospital, Los Angeles. Friday-Saturday. Contact: Daniel M. Hays, MD, Children's Hospital, P.O. Box 54700, Los Angeles 90054. (213) 660-2450, ext. 2675.

January 16-18—**Gynecologic Oncology.** Women's Hospital Medical Center at Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Sunday. 15 hrs. $200; $100, residents. Contact: Margaret Frederick, Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

January 19-23—**Cancer.** STAN. Monday-Friday.

January 28—**Lung Cancer.** Hospital of the Good Samaritan, Los Angeles. Wednesday. Contact: Janie Sternal, Coord., CME, Hospital of the Good Samaritan, 1212 Shatto St., Los Angeles 90017. (213) 482-8111.

February 27—**Breast Cancer.** UCSF at Childrens Hospital and Medical Center, San Francisco. Friday.

March 4-7—**Seminar on Modern Concepts in Oncology—4th Annual.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thursday-Sunday.

March 25-26—**Clinical Cancer Conference—11th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

March 26—**Colo-Rectal Carcinoma.** California Hospital Medical Center, Los Angeles. Friday. 10 hrs. $15. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

MEDICINE

January 11—**Ischemic Vascular Disease.** LLU at San Diego. Sunday.

January 16—**Current Concepts in Management of Thyroid Disorders.** Cedars-Sinai Medical Center at Mt. Sinai Hospital, Los Angeles. Friday. Contact: Linda Alperstein, Coord., CME, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 206.

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

January 20-23—**Internal Medicines and the Practice of Internal Medicine: 1976.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104 or Milton K. McDowell, MD, Col., MC, Asst. Chief, Dept. of Medicine, Letterman Army Medical Ctr., Presidio of San Francisco 94129.

February 5-6—**Contact Dermatitis.** STAN. Thursday-Friday.

February 14—**Annual Cardiology Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hospital, P.O. Box 1232, Fresno 93715.

February 16-20—**Topics in Internal Medicine. UCSD** at Town and Country Hotel, San Diego. Monday-Friday.

February 25-27—**Advances in the Diagnosis and Treatment of Pulmonary Disease.** California Thoracic Society at Sheraton-Harbor Island Hotel, San Diego. Wednesday-Friday. 20 hrs. $135 for members; $160, non-members. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 26-27—**Dermatologic Therapy for the Practicing Physician.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

February 26-28—**Pediatric Hematology.** See Pediatrics, February 26-28.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

February 27-28—**Pulmonary Artery Catheterization.** PMC. Fri.-Sat.

March 1-5—**Electrophysiology.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 4-5—**Diabetes.** USC at Good Samaritan Hospital, Los Angeles. Thursday-Friday.

March 4-6—**Cardiology '76—Practical Aspects of Cardiac Care.** American Heart Assn.-Golden Empire Chapter at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: AHA-Golden Empire Chapter, P.O. Box 16011, Sacramento 95816. (916) 444-8650.

March 5—**Diabetes—3rd Annual Program.** UCD at Red Lion Inn, Sacramento. Friday.

March 6—**Echocardiography Workshop.** PMC. Saturday.

March 11-13—**Cardiovascular Disease—1976: Practical Diagnosis and Management.** American College of Cardiology at La Costa Resort Hotel, San Diego. Thursday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 12—**Diagnosis and Treatment of Hypertension.** PMC. Friday.

March 20-21—**Theory and Practice of Echocardiography.** UCLA. Saturday-Sunday.

March 22-April 2—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26-27—**New Perspectives in Exercise Stress Testing.** American College of Cardiology; Memorial Hospital Medical Center, Long Beach; UCI at Center for Health Education, Memorial Hospital, Long Beach. Friday-Saturday. Contact: ACC, 9650 Rockville Pike, Bethesda, MD 20014.

March 30-April 2—**Consultant's Course in Dermatology.** UCSF. Tuesday-Friday.

OBSTETRICS AND GYNECOLOGY

January 16-18—**Third Neonatal Respiratory Symposium.** See Surgery and Anesthesiology, January 16-18.

January 16-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD at Sea Lodge, La Jolla. Friday-Monday.

January 17-24—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrical & Gynecological Society at Beverly Hilton Hotel, Los Angeles. Saturday-Sunday. 14 hrs. $45. Contact: Miss Dee Davis, Exec. Sec., L.A. Ob & Gyn Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 9-11—**Workshop in Perinatal Infections.** Kapiolani Hospital, Honolulu, Hawaii. Monday-Wednesday. $100. Contact: Wilma B. Schiner, RN, Dir. of Training & Education, Kapiolani Hospital, 1319 Punahou St., Honolulu 96814.

February 18-20—**Neonatal Medicine.** USC. Wednesday-Friday.

February 24-26—**Ob Infectious Diseases.** USC. Tuesday-Thursday.

March 5-7—**Obstetric Anesthesia Conference—Part I.** L.A. Obstetrical & Gynecological Society at Sheraton Airport Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

March 8-11—**Obstetric Anesthesia Conference—Part II.** L.A. Obstetrical and Gynecological Society at Sheraton-Maui Hotel, Maui, Hawaii. Monday-Thursday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

March 13—**Regional Perinatal Care Conference.** CMA at Hollywood Presbyterian Hospital, Hollywood. Saturday. Contact: George Feiler, CMA.

PEDIATRICS

January 8-11—**Winter Ski and Study Symposium—First Annual.** American Academy of Pediatrics, Calif. Chapter 2, at Mammoth Mountain. Thursday-Sunday. 14½ hrs. $125. Contact: AAP, Calif. Chapter 2, P.O. Box 2134, Inglewood 90305.

January 23-25—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 23-25.

January 24-25—**Down's Syndrome.** UCLA. Saturday-Sunday.

February 12—**Psycho-Social Aspects of Orofacial Clefts—4th Annual Cleft Palate Seminar.** See Of Interest To All, February 12.

February 18—**The Pediatrician's Obligation in the Atherosclerosis Epidemic.** American Heart Assn., Greater L.A. Affiliate, and L.A. Pediatric Society at Hyatt Regency Hotel, Los Angeles. Wednesday. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

February 21—**The Teenager's Doctor—A Key to Understanding Youth.** American Academy of Pediatrics, No. Calif. Chapter, at Children's Hospital, San Francisco. Saturday. 6 hrs. $25. Contact: Richard C. Brown, MD, Dept. of Pediatrics, Children's Hospital, 3700 California St., San Francisco 94119. (415) 387-8700.

February 26-28—**Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty Calori, CHMC, 51st & Grove Sts., Oakland 94609.

March 19-21—**Combined Southern California Pediatric Postgraduate Meeting: Clinical Pediatrics.** Calif. Chapter 2, District IX, American Academy of Pediatrics, at Riviera Hotel, Palm Springs. Friday-Sunday. Contact: Eve Black, Exec. Sec., P.O. Box 2134, Inglewood 90305.

PSYCHIATRY

January-April—**Intensive Review Course: American Board of Psychiatry and Neurology.** UCD at South Area Mental Health Center, Sacramento. Tuesdays, 7-10 p.m. 41 hrs.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** USC. Wednesdays, 10:00 a.m.-12:00 noon.

February 1-6—**Psychiatry Update: 2nd Annual Mid-Winter Program for Psychiatrists.** UCD at Bear Valley. Sunday-Friday.

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** Center for Counseling Skills, Kentfield, at Santa Barbara. Monday-Friday. Contact: Mrs. Tina Coffman, Extension Office, UCSB, Santa Barbara 93106.

February 21-22—**Introduction to Clinical Hypnosis and Behavior Modification.** UCLA at Americana Hotel, Los Angeles. Saturday-Sunday.

February 21-22—**Psychiatric Techniques in the Treatment of Drug Abuse and Alcoholism.** UCLA. Saturday-Sunday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** The Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** Center for Counseling Skills, Kentfield, at Palo Alto. Friday-Sunday. Contact: Center for Creativity and Growth, Suite 154, 770 Welch Rd., Palo Alto 94304. (415) 327-4477.

March 13-14—**Advanced Workshop in Hypnosis and Behavior Modification.** UCLA at Marina City Club, Marina Del Rey. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

January-May—**Ultrasound — Comprehensive Lecture Series.** USC. Weekly, 7:00-9:00 p.m., 20 consecutive weeks. Contact: Robert L. Wilson, MD, P.O. Box 1961, 1200 N. State St., Los Angeles 90033.

January 30-February 1—**Midwinter Radiological Conference—28th Annual.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Los Angeles Radiological Society, 15107 Vanowen St., Van Nuys 91405.

March 13-14—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 15-19—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 20-21—**Ultra Sound, A Practical Course.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 21-25—**Cardiac Radiology Refresher Course.** North American Society for Cardiac Radiology at Sir Francis Drake Hotel, San Francisco. Sunday-Thursday. Contact: Erik Carlsson, MD, Dept. of Radiology, UCSF.

SURGERY AND ANESTHESIOLOGY

January-April—**Intensive Review Course: American Board of Psychiatry and Neurology.** See Psychiatry, January-April.

January 7-March 17—**Intensive Review of Psychiatry and Neurology.** See Psychiatry, January 7-March 17.

January 8-9—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 9—**Vitreal and Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

January 9-10—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

January 10-17—**Super Seminar '76—First Annual Conference on the Foot and Ankle.** California College of Podiatric Medicine at St. Francis Hotel, San Francisco. One week. Contact: Super Seminar, P.O. Box 7855, Rincon Annex, San Francisco 94120.

January 11-17—**Otologic Surgery Course.** Ear Research Institute, Los Angeles. One week. 48 hours. $550; $350 for residents. Contact: F. H. Linthicum, Jr., MD, Dir. of Education, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 16-18—**Third Neonatal Respiratory Symposium.** California Society of Anesthesiologists at Marriott Hotel, Los Angeles. Friday-Sunday. Contact: Perinatal Anesthesia, P.O. Box 54508, Los Angeles 90054. (213) 226-3311.

January 17—**Vascular Disease—3rd Annual Symposium.** UCSD at UC Medical Center, San Diego. Saturday.

January 21-23—**Sierra Traumatological Society—5th Annual Meeting.** See Of Interest To All, January 21-23.

January 23-25—**Pediatric Anesthesiology—14th Clinical Conference.** Childrens Hospital of L.A. at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100. Contact: Wayne Herbert, MD, CHLA, P.O. Box 54700, Los Angeles 90054. (213) 663-3341, ext. 2262.

January 25-30—**Postgraduate Institute on Emergency Medicine.** See Of Interest To All, January 25-30.

January 26-30—**Topics in Emergency Medicine.** See Of Interest To All, January 26-30.

January 28-30—**Advances in Neurology.** UCSF. Wednesday-Friday.

February 1-4—**Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday.

February 5-6—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 6—**Photocoagulation Therapy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

February 11-13—**Clinical Applications of Vitreous Surgery.** USC. Wednesday-Friday.

February 12-15—**Symposium on Controversial Areas in Surgery of the Head and Neck—5th Annual.** UCSD. Thursday-Sunday. Contact: UCSD or Alan M. Nahum, MD, University Hospital, 225 W. Dickinson, San Diego 92103.

February 13-14—**Phacoemulsification Conference.** St. Mary's Hospital and Medical Center, San Francisco. Friday-Saturday. Contact: J. Albert Sarrail, MD, 450 Sutter St., San Francisco. (415) 397-1500.

March 5—**Strabismus Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Friday. Contact: Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles.

March 5-7—**Obstetric Anesthesia Conference, Part I.** See Obstetrics and Gynecology, March 5-7.

March 6-7—**American Society of Anesthesiologists Workshop.** Sheraton-Harbor Island Hotel, San Diego. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068.

March 8-11—**Obstetric Anesthesia Conference, Part II.** See Obstetrics and Gynecology, March 8-11.

March 9-13—**Seminar on Controversial Areas in Surgery—13th Annual.** UCLA at Canyon Hotel, Palm Springs. Tuesday-Saturday.

March 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 12-13—**Hand Injuries and Infections.** PMC. Friday-Saturday.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma—3rd Annual.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday.

March 14-26—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 17-21—**Symposium on Vascular Surgery—4th Annual.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 18-19—**Diseases of the Urinary Tract—4th Annual Symposium.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday.

March 22-26—**Trauma and Surgical Emergencies.** STAN. Monday-Friday.

March 27-29—**Developmental and Acquired Jaw Problems.** UCLA. Saturday-Monday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

January 8-9—**New and Old Antibiotics.** USC. Thursday-Friday.

January 21-23—**Sierra Traumatological Society—5th Annual Meeting.** Kirkwood Meadows. Wednesday-Friday. Contact: William E. Latham, MD, Sierra Traumatological Society, P.O. Box 230, Stockton 95201. (209) 466-9535.

January 21-24—**The Physician and the Hospital.** USC at Canyon Hotel, Palm Springs. Wednesday-Saturday.

January 23-24—**Management of Stress in the Middle Years.** Vista Hill Foundation at Hilton Inn, San Diego. Friday-Saturday. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123.

January 24-25—**Ways of Healing: Ancient and Modern.** Institute for the Study of Human Knowledge and UCSF at Sheraton-Palace Hotel, San Francisco. Saturday-Sunday. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, C135G, UCSF. (415) 666-2894.

January 25-30—**Postgraduate Institute on Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sunday-Friday.

January 26-30—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 2-7—**Family Practice Review Course—7th Annual.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 6-11—**California Medical Association—105th Annual**

Session. Hyatt Regency Hotel, San Francisco. Friday-Wednesday.

February 10-14—**Autogenics Training Techniques Workshop.** UCLA at Lake Arrowhead. Tuesday-Saturday.

February 11-13—**Course for Physicians in Family Practice—26th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $100. Contact: Alan J. Coleman, MD, Assoc. Chief of Medicine, Mt. Zion Hospital, 2511 Bush St., San Francisco 94115. (415) 929-1122.

February 12—**Psycho-Social Aspects of Orofacial Clefts—4th Annual Cleft Palate Seminar.** Cleft Palate Team, Rancho Los Amigos Hospital; USC; L.A. County Nat'l Foundation March of Dimes at Rancho Los Amigos Hospital, Downey. Wednesday. Contact: Cleft Palate Service, Rancho Los Amigos Hosp., 7601 E. Imperial Highway, Downey 90242. (213) 922-7454.

February 13-14—**Diving Medicine for Practicing Physicians.** UCSF at Holiday Inn-Union Square, San Francisco. Friday-Saturday.

February 15-19—**Sports Medicine for Primary Physicians.** Univ. of Hawaii School of Medicine at North Shore of Oahu, Hawaii. $200. Sunday-Thursday. Contact: Richard H. Strauss, MD, Univ. of Hawaii Conference Ctr., 2500 Dole St., Honolulu 96822.

February 16-20—**Treating Distressed Couples: The Masters and Johnson Method.** See Psychiatry, February 16-20.

February 20—**Total Parenteral Nutrition Workshop.** UCD at Red Lion Inn, Sacramento. Friday.

February 27-29—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, February 27-29.

February 28-29—**Infectious Disease and Pulmonary Disease for Family Practitioners.** UCLA. Saturday-Sunday.

March 1-5—**Basic Science for Clinicians.** STAN. Monday-Friday.

March 5-7—**Current Therapy for Marital-Sexual Dysfunction.** See Psychiatry, March 5-7.

March 7-11—**LLU Alumni Postgraduate Convention.** Sunday-Thursday.

March 12—**Diagnosis and Treatment of Hypertension.** See Medicine, March 12.

March 13-17—**Multidiscipline Symposium and Workshop on Management of Trauma.** See Surgery, March 13-17.

March 19—**Office Management of Parkinsonism.** PMC at Miyako Hotel, San Francisco. Friday.

March 22-26—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 26-27—**Use of Ventilators.** PMC. Friday-Saturday.

March 29-April 2—**Basic and Applied Pharmacology.** STAN. Monday-Friday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Providence Medical Center, Auditorium, Providence Hall, 700 N.E. 47th Avenue, Portland, 97213

December 10—**Grans vs. Scans in Diagnosis of Pulmonary Thromboembolic Disease.**

December 17—**Hepatitis A, Hepatitis B, and Thee.**

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:
Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

December 12-13—**Clinical Problems in Endocrinology.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle.

9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 9-10—**Laboratory Investigations in Gastrointestinal Disease.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 16—**Continuing Education Course in Pulmonary Disease.** Friday. Mount Vernon Town and Country Motor Inn, Mount Vernon, WA. 6 hrs. $10. Contact: Dave Chivers, Washington Lung Association, 216 Broadway East, Seattle 98112. (206) 329-4411.

January 22-23—**Pediatric Allergy and Immunology.** Thursday-Friday. Univ. of Wash., Child Development and Mental Retardation Center, Seattle. Hours and fees to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 27-30—**Medical-Ski Conference.** Tuesday-Friday. Big Mountain, MT. Contact: R. D. Buchanan, MD, P.O. Box 220, Columbia Falls, MT 59912.

January 30-31—**Tax, Estate and Financial Planning for Physicians.** Friday-Saturday. Olympic Hotel, Seattle. Limited to 50 physicians and spouses. 12 hrs. $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. School of Med., Seattle 98195. (206) 543-1050.

February 5-7—**Stroke Symposium.** Thursday-Saturday. Washington Plaza Hotel, Seattle. 12 hrs. Physicians, $40; others, $25. Contact: Northwest Hospital, 1551 North 120th, Seattle 98133. (206) EM 4-0500.

February 6-12—**Critical Care: Maternal and Perinatal.** Friday-Thursday. Sun Valley, Idaho. 21 hrs. MDs, PhDs, $100; others, $75. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

February 12-13—**14th Annual Symposium on Respiratory Disease.** Friday-Saturday. Olympic Hotel, Seattle. 14 hrs. $15. Contact: Ms. Jo Senters, Washington Lung Association, 216 Broadway East, Seattle 98102. (206) 322-7110.

February 18-19—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Longview, 18; Olympia, 19. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050.

March 5-6—**Recent Advances in Renal Disease—27th Annual Spokane Society of Internal Medicine Scientific Session.** Friday-Saturday. Sheraton Hotel, Spokane, WA. AAFP credit approved. Contact: Thomas A. Marr, MD, 312 W. 8th, Spokane, WA 99204. (509) 838-2531.

March 9-10—**Treating the Untreatable—Univ. of Washington School of Medicine's Western Washington Circuit Course.** Port Angeles, 9; Everett, 10. 4 hrs. Physicians, $25; others, $10. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 12-13—**Orthopedic Disease: A Practical Approach to Clinical Management.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

March 15-19—**Emergency Medicine Institute.** Monday-Friday. Univ. of Wash. Sch of Med., Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 18-19—**American Society of Clinical Pharmacology and Therapeutics.** Thursday-Friday. Washington Plaza Hotel, Seattle. Contact: E. H. Funk, MD, 1718 Gallagher Rd., Norristown, PA 19401. (215) 277-3831.

March 18-19—**Evaluation and Management of Behavior Problems in the Elderly.** Thursday-Friday. Seattle. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 22-26—**Advances in Family Practice.** Monday-Friday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Approximately 35 hrs. $100. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, SB-62, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

March 25-26—**Immediate Care of the Sick and Injured.** Thursday-Friday. Univ. of Wash. Sch. of Med. Hours and fee to be determined. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 14-23—**Tax, Estate and Financial Planning.** Friday-Monday. Aboard the SS Rotterdam; 7-day cruise to Nassau and Bermuda. 25 hrs. $200. Contact: Richard L. Reimer, Asst. Dir. CME, T287 HSB, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Armour Pharmaceutical Company
Letter 5
Ayerst Laboratories
Premarin 6, 7
Books Received 12
Classified 20, 29
Compton Foundation 20
Coulter Electronics Inc. 8
Dairy Council of California 16
Endo Laboratories Inc.
Percodan 11
Eli Lilly and Company
Darvon-N 100 and Darvon Compound-65 ..... 8, 9
Keflex 24
Merck Sharp & Dohme
Triavil 26, 27, 28
Pharmaceutical Manufacturers Association 14, 15
Presto Food Products Inc.
Mocha Mix 19
A. H. Robins Company
Dimetapp 17
Phenaphen with Codeine 18
Roche Laboratories
Valium ..... 2nd Cover and Page 1
William H. Rorer, Inc.
Maalox ..... 4th Cover
W. B. Saunders Company 21
G. D. Searle & Co.
Lomotil 4, 5
Security Pacific Bank 3
Smith Kline & French
Dyazide ..... 3rd Cover
Warner Chilcott Laboratories
Proloid 12, 13
Wells Fargo Bank 25
Wyeth Laboratories
Bicillin/Wycillin 22, 23
Ovral 10

X77-361

Western journal of medicine.
v.123, 1975.

SENIOR

DATE	ISSUED TO
JAN 21 '77	[illegible]
MAR 16	Amelia J. Davis 213-58-5109
MAR 25 '77	Paul Stern 214-60-0198
MAY 7 '77	[illegible]

X77-361

Western journal of medicine.
v.123, 1975.

RETURN THIS BOOK ON OR BEFORE LAST DATE STAMPED

FEB 4 '77
JAN 21 '77
RET'D. AUG 18 '78
MAR 16 '77
RET'D. MAR 15 '77
MAR 25 '77
RET'D. MAR 25 '77
MAY 7 '77
RET'D. MAY 2 '77
MAY 27 1977
RET'D. MAY 27 '77
JUL 13 '77
JUL 18 '77
APR 12 '78
RET'D. APR 10 '78
AUG 24 '78
NOV 7 '78
RET'D. OCT 31 '78
NOV 17 '78
RET'D. NOV 20 '78